

# EXHIBIT

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*Polymer Science and Materials Chemistry*

Exponent<sup>®</sup>

**Expert Report of  
Dr. Steven MacLean**

**UNITED STATES DISTRICT COURT  
FOR THE SOUTHERN DISTRICT OF  
WEST VIRGINIA  
CHARLESTON DIVISION**

**This document relates to:**  
***Ethicon Inc., Pelvic  
Repair System Products  
Liability Litigation***



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Dr. Steven MacLean**

**UNITED STATES DISTRICT COURT  
FOR THE SOUTHERN DISTRICT OF  
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CHARLESTON DIVISION**

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## Contents

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	<u>Page</u>
<b>List of Figures</b>	<b>4</b>
<b>List of Tables</b>	<b>5</b>
<b>Limitations</b>	<b>6</b>
<b>Steven MacLean, Ph.D., P.E. Bio</b>	<b>7</b>
<b>Polypropylene</b>	<b>10</b>
Chemical Structure of Polypropylene	10
Crystallinity	11
Molecular Weight	12
Thermal Properties of Polypropylene	12
Manufacturing of Polypropylene Resins	13
Processing of Polypropylene Fibers	13
Polypropylene Applications	14
<b>Chemistry of Oxidation and Formaldehyde Fixation</b>	<b>15</b>
Oxidation of Polypropylene	15
Formaldehyde-Protein Crosslinking	17
<b>PROLENE</b>	<b>19</b>
Composition	19
PROLENE Biocompatibility	20
<b>Mesh as a Medical Device</b>	<b>22</b>
Introduction to Surgical Mesh	22
Current Surgical Mesh Materials	22
Suture and Mesh Literature Review	24
Clavé	24
De Tayrac	25
Costello	26

**Attorney Client Privilege—September 15, 2015**

Cozad	28
Liebert	30
Mary	30
Wood	31
Guelcher	32
<b>Artifacts in Microtome Processing</b>	<b>33</b>
<b>Ethicon’s Investigation</b>	<b>35</b>
Microcrack Committee Investigation	35
Microscopy	35
Mechanical Testing	36
Melting Point Analysis	36
FTIR Analysis	37
Seven Year Dog Study	39
Study Protocol	39
Study Results	40
Conclusion	46
<b>Rebuttal of Plaintiff Experts</b>	<b>47</b>
Iakovlev	47
Jordi	53
Guelcher	58
<b>Conclusion and Opinions</b>	<b>61</b>
<b>Appendix A</b>	<b>1</b>
Steven MacLean, Ph.D., P.E. CV	1
Professional Profile	1
Academic Credentials and Professional Honors	2
Licenses and Certifications	2
Publications	2
Presentations	4
Prior Experience	5
Professional Affiliations	5
<b>Appendix B</b>	<b>6</b>
Testimony of Steven MacLean, Ph.D., P.E.	6

**Attorney Client Privilege—September 15, 2015**

<b>Appendix C</b>	<b>7</b>
List of Documents Reviewed	7
<b>Appendix D</b>	<b>21</b>
Compensation	21

## List of Figures

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	<u>Page</u>
Figure 1. A.) Chemical structure of propylene and B.) Generalized chemical structure of linear polypropylene.	10
Figure 2. The three most common stereoregular conformations of polypropylene, isotactic (top), syndiotactic (middle), and atactic (bottom).	11
Figure 3. Reported oxidation reaction pathway of polypropylene. <sup>9</sup>	16
Figure 4. Simplified reaction schematic of proteins with formalin.	18
Figure 5. Chemical structure of dilaurylthiodipropionate A.), oxidized polypropylene <sup>1</sup> B.), formaldehyde crosslinked proteins <sup>14</sup> C.), a peptide bond, which make up proteins D.) and a fatty acid ester <sup>78</sup> E.). All of these molecules have functional groups which contain carbonyls (circled in red).	38
Figure 6. Simplified illustration of the ventral area of a dog torso, showing the location of the six suture implantation sites.	40
Figure 7. Schematic stress-strain curves for a non-plasticized and a plasticized material. Note the increase in toughness (area under the stress-strain curves) due to plasticization.	43
Figure 8. Summary of tensile tests performed on ETHILON, Novafil, PROLENE and PVDF sutures in Ethicon's seven year dog study.	45
Figure 9. Cross-sectional schematic and calculated theoretical total molecular weight (Mn) of excised 5-0 PROLENE sutures from Ethicon's seven year dog study using Dr. Jordi's surface melting temperature to calculate Mn of the crust layer (note: dimensions are not to drawn to scale).	55

## List of Tables

---

	<u>Page</u>
Table 1. Molecular weight of exemplar PROLENE compared to explanted PROLENE sutures after 7 years <i>in vivo</i> .	42
Table 2. Summary of suture surface examinations. The number of sutures exhibiting damage (transverse cracking, longitudinal cracking, scratches, etc.) and the total number of sutures of each type after one, two, five and seven years <i>in vivo</i> .	46

## **Limitations**

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At the request of Butler Snow LLP, Exponent reviewed relevant scientific literature, historic documented studies and expert reports for the pending litigation. Exponent investigated specific issues relevant to this report as requested by the client. The scope of services performed during this investigation may not adequately address the needs of other users of this report, and any reuse of this report or its findings, conclusions, or recommendations is at the sole risk of the user. The opinions and comments formulated during this investigation are based on observations and information available at the time of the investigation.

The findings presented herein are made to a reasonable degree of engineering certainty. We have endeavored to be accurate and complete in our assignment. If new data becomes available, or there are perceived omissions or misstatements in this report, we ask that they are brought to our attention as soon as possible so that we have the opportunity to address them.

## **Steven MacLean, Ph.D., P.E. Bio**

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I am a Senior Managing Engineer in the Polymer Science and Materials Chemistry Practice at Exponent Failure Analysis Associates, Inc. (“Exponent”). My expertise and experience includes the chemical and physical behavior of polymeric materials in end-use applications, specifically in the evaluation of polymeric components in product safety assessments and product failure analysis. I have a B.S. and M.E. in Mechanical Engineering from Rensselaer Polytechnic Institute, and a M.S. in Material Science and Engineering from Rochester Institute of Technology. I also obtained a Ph.D. in Material Science from the University of Rochester in 2007. I am a registered Professional Engineer in New York and Maryland, a Senior Member of the Society of Plastics Engineers (SPE), and a board member of SPE’s Failure Analysis and Prevention Special Interest Group.

During the pursuit of my advanced degrees in materials science, my chosen field of study was polymer science and engineering. Graduate courses taken during my academic career that specifically focused on polymers included, but were not limited to, polymer science, organic polymer chemistry, polymer physics, polymer rheology, polymer processing, bulk physical properties of polymers, adhesion theory, and analytical techniques for polymeric materials. Supplemental course work included mechanics of materials, fracture mechanics, thermodynamics of materials and electron microscopy practicum. At the master’s degree level, my polymer research included characterizing the changes in chemical and physical properties of polycarbonate due to multiple heat histories from processing. At the doctoral level, my polymer research was focused on developing and investigating novel formulations of rubber-toughened polyphenylene ether polymers for use in pressurized, potable water systems. The primary emphasis of my dissertation included quantifying changes in select mechanical properties, including fracture toughness and tensile properties, due to the degrading effects from persistent exposure to chlorinated water at elevated temperatures.

In addition to my academic education and training, I have also been actively practicing in the field of polymer science and engineering for the past 20 years. Throughout that time, I have routinely utilized numerous polymer characterization techniques including, but not limited to, infrared spectroscopy, chromatography, mass spectrometry, calorimetry as well as optical,

scanning electron and transmission electron microscopy. In particular, I have used these microscopic techniques to examine the topography and morphology of fracture surfaces created as a result of polymer cracking. I have also employed these techniques to characterize modes of polymer failure such as creep, fatigue, stress overload and environmentally-assisted stress cracking. In many instances, I have published the use of these analytical techniques to investigate polymer failures in commercialized products in peer-reviewed journal articles and scientific conference proceedings.

Prior to joining Exponent in 2011, I worked for over 15 years at General Electric Plastics (GE) and SABIC Innovative Plastics (SABIC) in a variety of technical roles of increasing responsibilities. Throughout my tenure, I was routinely involved in material selection, performance and testing for, among other things, high-demand applications, product safety assessments, and product failure analysis. As a result I have significant expertise and experience with industry standards and applicable regulations that prescribe the technical performance of polymeric materials in end-use applications, including those in the medical device industry.

At GE Plastics, I was trained extensively in the Six Sigma quality process, and became certified as a Six Sigma Black Belt. As a Certified Six Sigma Black Belt, my responsibilities included improving business processes by employing a variety of well-established statistical methods as well as mentoring and training Six Sigma Green Belts throughout the company.

Throughout my career, I have evaluated the suitability and performance of polymeric materials in end-use applications, including specifically, for the medical device industry. While at GE and SABIC, I worked with numerous medical device companies on material development, material specification, design and manufacturing for a wide variety of medical device applications. These efforts included, inter alia, developing and implementing tests related to the bulk physical properties of polymeric materials specified in said devices as well as material formulation development to meet unique device requirements that could not be met with off-the-shelf grades of resin. Formulation development often included the selection and refinement of base polymers or alloys, molecular weight, additives, stabilizers, processing aides, lubricants, colorants and inorganic fibers and fillers. In addition to proactive design and material selection assistance, I have worked on hundreds of product safety assessments and failure analyses

involving polymeric materials, many of which were performed on medical devices and components.

In my prior role as Director of Global Agency Relations and Product Safety at GE/SABIC, part of my leadership responsibilities included being an active member of the business' Healthcare Resins Advisory Board. The board developed internal processes and standards for the specification, use and sale of GE/SABIC resins in medical device applications. These efforts included ensuring that commercial resin grades within the GE/SABIC healthcare portfolio were assessed for biocompatibility using industry accepted test protocols such as United States Pharmacopeia (USP) Class VI, Tripartite Biocompatibility Guidance or ISO 10993 Biological Evaluation of Medical Devices standards. For the past several decades, the latter two standards have been supported by the Food and Drug Administration (FDA) and commonly employed to assess the potential for cytotoxicity, hemolysis, pyrogenicity, sensitization issues, among other biological effects, when the human body is exposed to foreign materials. In addition, the board also ensured that "good manufacturing processes" were globally implemented to maximize the purity levels of all compounded materials within the healthcare resin portfolio.

In addition to my relevant training, education and industry experience, I have also reviewed and synthesized the available public literature pertaining to *in vivo* and *in vitro* studies of polymeric mesh devices, long-term implantation of polymeric medical devices, foreign body response to implantable materials, as well as select plaintiff reports which allege *in vivo* PROLENE mesh degradation. A complete list of the reviewed literature can be found in Appendix C.

## Polypropylene

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### Chemical Structure of Polypropylene

Polypropylene is a widely produced polymer which possesses an excellent balance of physical properties, processability, and cost-effectiveness and is commonly specified for use in a wide range of commercial applications.<sup>1</sup> Polypropylene is formed via a polymerization reaction where propylene molecules (monomers) are combined together in a step-wise fashion to ultimately form linear, chain-like macromolecules (Figure 1A). Polymerization is achieved through breaking the unsaturated (double) bond in propylene, and covalently reacting this bond with the polymer chain. In the current day commercial production of polypropylene, Ziegler-Natta or metallocene catalysts facilitate this reaction.<sup>1</sup> Polypropylene is most commonly produced as a linear polymer (Figure 1B), meaning that the propylene monomers bond to the polymer at the end of the polymer chain, as opposed to forming a branching molecular architecture.<sup>1</sup>

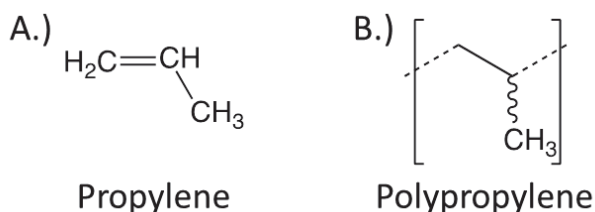


Figure 1. A.) Chemical structure of propylene and B.) Generalized chemical structure of linear polypropylene.

Polypropylene is a vinyl polymer with a lone pendant methyl groups in its repeat unit as shown in Figure 1B. Chain growth using these catalysts is designed to attach in a head-to-tail manner such that the pendant methyl groups are regularly spaced.<sup>1</sup> The collective orientation of these groups with respect to the backbone of the polymer, known as stereoregularity, can affect the final physical properties of the polymer.<sup>1,2</sup> As shown in Figure 2, the pendant methyl groups can

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<sup>1</sup> Maier, C., Calafut, T. *Polypropylene: The Definitive User's Guide and Databook*. Norwich, NY: Plastics Design Library, 1998.

<sup>2</sup> Odian, G. G. *Principles of polymerization*, 4th ed.; Wiley-Interscience: Hoboken, N.J., 2004.

be oriented in two different directions with respect to the polymer backbone, allowing polypropylene to be produced in three different stereoregular conformations: isotactic (pendant methyl groups along the same side), syndiotactic (alternating sides), or atactic (random orientation). Control over which type of stereoregularity the polymer adopts is determined primarily by the choice of catalyst.<sup>1,2</sup> The majority of commercial polypropylene is manufactured in the isotactic conformation (*iso*-polypropylene).<sup>1</sup>

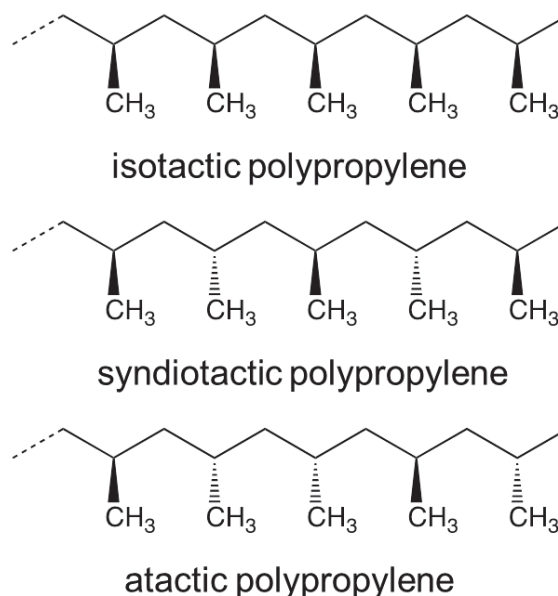


Figure 2. The three most common stereoregular conformations of polypropylene, isotactic (top), syndiotactic (middle), and atactic (bottom).

## Crystallinity

Polypropylene is semi-crystalline in nature, meaning that both amorphous and crystalline regions are present throughout the polymer matrix. A typical range for the degree of crystallinity is 20% to 40% for commercially available *iso*-polypropylene.<sup>3</sup> The degree of crystallinity of the product is mainly determined by the stereoregularity and processing conditions. Isotactic polypropylene (*iso*-polypropylene) is the most crystalline conformation, due to the collective orientation of the pendant groups in the same direction allowing for neighboring polymer molecules to align and form a compact, ordered structure. The degree of crystallinity achieved

<sup>3</sup> Sastri, V. R. "Commodity Thermoplastics." *Plastics in Medical Devices*. Elsevier, 2014. 73–120.

by the material in its solid state directly influences bulk physical and thermodynamic properties.<sup>1</sup> With regards to expected mechanical properties, a higher crystallinity generally results in increased stiffness, yield stress, Young's modulus, and flexural strength among others, but a decreased toughness and impact strength.<sup>1</sup>

## Molecular Weight

During synthesis, propylene monomers are converted into polypropylene macromolecules of differing lengths. The lengths of polymeric chains are defined by the number average ( $M_n$ ) and weight average ( $M_w$ ) molecular weights. Typical  $M_w$  values for commercial polypropylene vary from 220,000 -700,000 g/mol<sup>1</sup> depending on a number of variables including the specific catalyst used.

Since there is a degree of randomness associated with the synthesis of most commercial polymers, the total number of monomeric units contained within each polymer chain will vary within a given sample. This range of polymer chain lengths is referred to as the molecular weight distribution (MWD) and is commonly reported as the polydispersity index (PDI). The PDI of a polymer is defined as the quotient of  $M_w$  and  $M_n$  ( $M_w/M_n$ ) and is a measure of the broadness of the MWD, with a larger PDI corresponding to a broader MWD. Typical PDI values range from 2.1 – 11.0 for commercial polypropylene.

Molecular weight and MWD directly influence the mechanical properties and processability of the bulk polymer.<sup>1</sup> Polypropylene resins with a larger PDI are more shear sensitive, meaning the apparent melt viscosity decreases at a faster rate with increasing shear rate.

## Thermal Properties of Polypropylene

Thermoplastic materials, including all variants of polypropylene, possess thermal transition temperatures that characterize the thermodynamic behavior of the polymer. These thermodynamic transitions are primarily based on the unique molecular structure and order of a specific polymer. The first of such thermal properties is the glass transition temperature,  $T_g$ ,

which is the temperature at which a polymer shifts from its glassy (more solid-like) phase to its rubbery phase. Typical  $T_g$  values for polypropylene range from -35 to 26°C.<sup>1</sup>

The temperature at which crystalline domains are destroyed is known as the polymer's melting point ( $T_m$ ). Once  $T_m$  has been eclipsed, the material's viscosity is sharply reduced and has the ability to readily flow in the presence of driving forces such as pressure or stress. Melting points for polypropylene can vary from 171°C for perfectly isotactic polypropylene to 130°C for syndiotactic polypropylene.<sup>1</sup> In practice, commercially produced *iso*-polypropylene typically melts between 160-166°C due to small regions of atacticity (i.e. noncrystallinity).<sup>1</sup>

## Manufacturing of Polypropylene Resins

Industrial synthesis of bulk polypropylene is generally performed using either a bulk slurry (e.g. the Borstar® process or the Spheripol® process), or a gas phase reaction with a solid catalyst bed (e.g. Novolen®, Unipol® PP processes).<sup>4,5</sup> Depending on its end use, the polypropylene resins are then mixed with additives and stabilizers to aid in processing, provide color, enhance mechanical properties, or combat thermal or oxidative degradation. These additional formulation ingredients can be compounded into the finished polypropylene product either in batch mixing, or through continuous mixing (e.g. extrusion).

## Processing of Polypropylene Fibers

Polypropylene has melt flow properties that make it well suited for the production of synthetic fibers.<sup>1</sup> Polypropylene fibers are commonly produced via melt spinning, where the polypropylene is melted and extruded through a spinneret followed by cooling and solidification.<sup>1</sup> The process of drawing a polypropylene fiber from the melt exerts uniaxial force on the polymer chains which, after cooling and solidification, results in the polymer chains being preferentially oriented along the drawing axis (i.e. the fiber length). Therefore, the crystalline character in polypropylene fibers is not only dependent on the rate of cooling during

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<sup>4</sup> “*Process Analytics in Polypropylene (PP) Plants*”, Siemens AG; 2007, pp:1-9.

<sup>5</sup> Mei, G.; Herben, P.; Cagnani, C.; Mazzucco A. *The Spherizone Process: A New PP Manufacturing Platform*, Macromol. Symp. 2006, 245–246, 677–680.

melt spinning but also on the induced molecular orientation from the mechanical drawing process.<sup>6</sup>

## Polypropylene Applications

Numerous grades of resin with varying properties make polypropylene useful in a wide array of applications including components and devices for the medical industry, injection molded parts for the automotive industry, and other consumer products.<sup>1</sup> Its ubiquitous specification and use is largely due to its excellent balance of bulk physical properties, ease of processing, chemical resistance and ability to withstand moderate to elevated thermal environments.<sup>1</sup> In addition, polypropylene is generally unaffected when in contact with most solvents, acids, bases, disinfectants, and other common chemicals, which make it an excellent candidate material for many industries, including medical applications.<sup>3</sup>

Polypropylene has found use in numerous applications, including medical devices, textiles, vehicle components and packaging.<sup>1</sup> Polypropylene also finds wide usage in small medical equipment, mainly in hypodermic syringes,<sup>3</sup> but also in medical tubing, trays, sutures, vials and many others. The widespread use of polypropylene in the medical industry stems from its chemical resistance, mechanical strength, biocompatibility, ability to be sterilized, colorability and clarity.<sup>3</sup> As a result, it has become a common material substitution for glass and other polymeric materials in the medical industry. Specifically in the case of sutures, polypropylene fibers are now a common material choice because of these desirable properties.<sup>3</sup>

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<sup>6</sup> Salem, D. R. *Structure Formation in Polymeric Fibers*. Munich : Cincinnati: Hanser Gardner Publications, 2001.

## Chemistry of Oxidation and Formaldehyde Fixation

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### Oxidation of Polypropylene

Despite its semi-crystalline nature, polypropylene, in its neat form, can be susceptible to oxidation in its amorphous regions. Specifically, oxidation occurs at the pendant methyl groups present on the polymer backbone.<sup>1</sup> Polypropylene can oxidize as a result of exposure to heat, oxygen in the air, acid and basic environments, radiation and UV light.<sup>1,7,8</sup> The energy associated with any of these environments has the potential to break the bonds between a tertiary carbon atom and a neighboring hydrogen atom, resulting in the formation of radicals. These radicals are generally reactive and, in the presence of oxygen, can form hydroperoxides that eventually lead to the formation of carbonyl groups in the form of carboxylic acids, lactones, aldehydes, and esters (Figure 3).<sup>1,9</sup>

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<sup>7</sup> Rosato, D. V., Mattia, D. P., Rosato, D. V. *Designing with Plastics and Composites: A Handbook*. Boston, MA: Springer US, 1991.

<sup>8</sup> Wieslawa Urbaniak-Domagala. *The Use of the Spectrometric Technique FTIR-ATR to Examine the Polymers Surface*. INTECH Open Access Publisher, 2012.

<sup>9</sup> Gijsman, P., Hennekens, J., Vincent, J. The Mechanism of the Low-Temperature Oxidation of Polypropylene. *Polym. Degrad. Stab.*, (1993) 42(1):95–105.

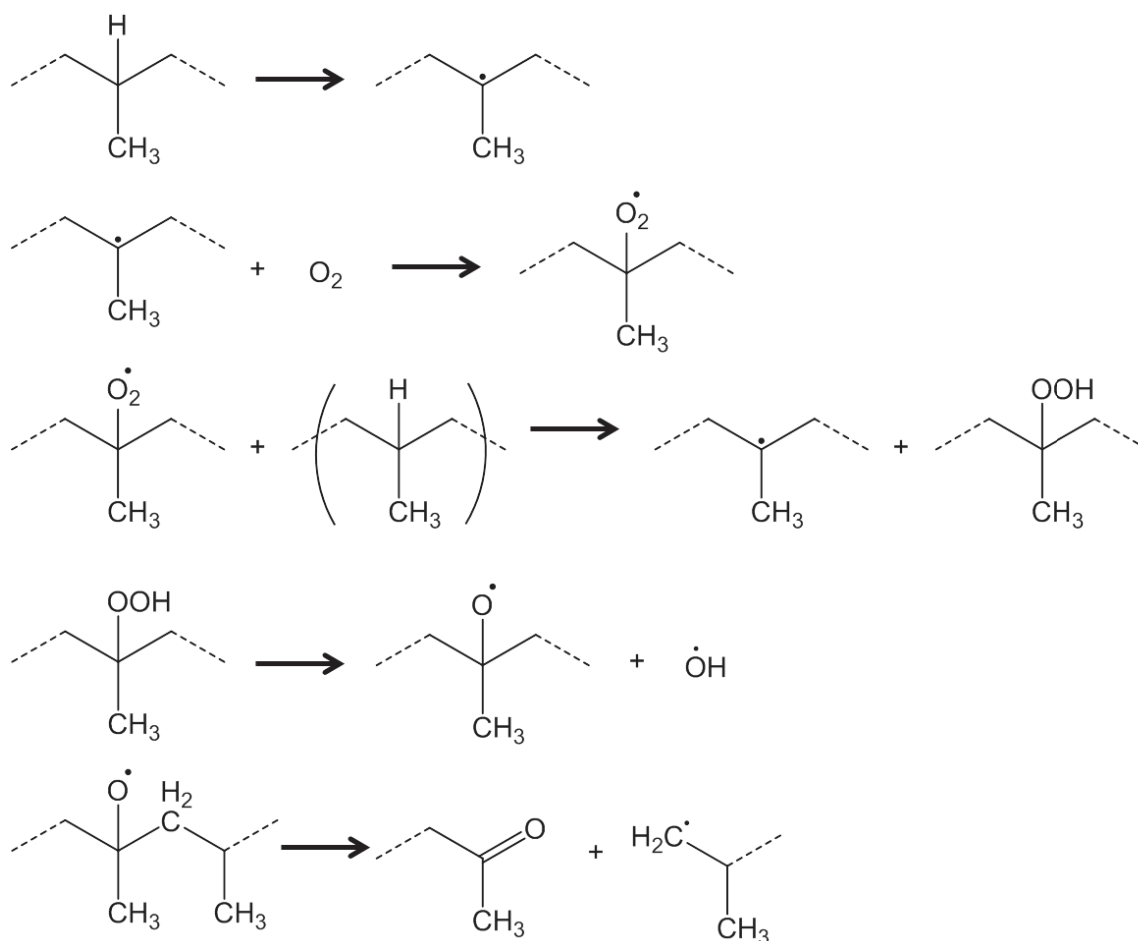


Figure 3. Reported oxidation reaction pathway of polypropylene.<sup>9</sup>

As a result of oxidation, chemical, physical, and mechanical changes may occur in polypropylene. The potential chemical changes consist not only of the formation of carbonyl containing groups, but also a loss in average molecular weight and shifts in molecular weight distribution. Radicals formed during the oxidation process in polypropylene can lead to chain scission resulting in a reduction in molecular weight.<sup>1</sup> Oxidation in polypropylene can also change the physical properties and appearance of the polymer. Polypropylene can turn “yellow-brown” in color and start to “flake away” after it begins to become oxidized.<sup>10</sup> Furthermore, the mechanical properties can also change as polypropylene becomes oxidized.<sup>11</sup> In general, it

<sup>10</sup> *Additives: Antioxidants*. Equistar. p:1–2.

<sup>11</sup> Gensler, R., Plummer, C. J.G., Kausch, H.-H., Kramer, E., et al. “Thermo-Oxidative Degradation of Isotactic Polypropylene at High Temperatures: Phenolic Antioxidants versus HAS.” *Polym. Degrad. Stab.*, (2000) 67(2):195–208.

becomes more brittle as evidenced by a reduction in its elongation-at-break (ductility) when tensile tested.

In virtually all engineering applications, antioxidants are used to combat oxidation in polypropylene. These antioxidants are chemical additives which are added to the resin prior to processing and are typically divided into two groups known as primary and secondary antioxidants. Primary antioxidants are radical scavengers which are typically hindered phenolics and secondary aromatic amines.<sup>1,10</sup> These additives react with radicals and hydroperoxides in the polypropylene, thus eliminating the radicals from the polymer. The result is primary antioxidant species containing radicals, which are more stable than the polypropylene radical. Secondary antioxidants are peroxide decomposers which are typically phosphites and thioesters.<sup>1,10</sup> These additives react with peroxides to form more stable alcohols. Often, both primary and secondary antioxidants are used together to protect polypropylene from oxidation

## Formaldehyde-Protein Crosslinking

Chemical fixation of tissues is a common technique used in histology for purposes of preservation and hardening.<sup>12,13</sup> While a number of different chemical fixatives are used in histology, formaldehyde is one of the most common.<sup>12</sup> Formalin (a formaldehyde/water mixture) was first used to harden tissues in 1893 and has been widely accepted chemical fixative since.<sup>14</sup> Formaldehyde works as a fixative by chemically cross-linking proteins, forming a large network polymer. The cross-linking chemical reaction in tissue between formaldehyde and proteins is outlined in Figure 4.<sup>13</sup> Formaldehyde can react with amino acid chains in proteins to form methylene bridges between polypeptide chains.<sup>12,13,14</sup>

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<sup>12</sup> Hewitson, T. D., Wigg, B., Becker, G. J. "Tissue Preparation for Histochemistry: Fixation, Embedding, and Antigen Retrieval for Light Microscopy." *Histology Protocols*. Ed. Tim D. Hewitson and Ian A. Darby. Vol. 611. Totowa, NJ: Humana Press, 2010. 3–18.

<sup>13</sup> Thavarajah, R., Mudimbaimannar, V., Rao, U., Ranganathan, K., et al. "Chemical and Physical Basics of Routine Formaldehyde Fixation." *J. Oral Maxillofac. Pathol.*, (2012) 16(3):400–405.

<sup>14</sup> Puchtler, H., Meloan, S. N. "On the Chemistry of Formaldehyde Fixation and Its Effects on Immunohistochemical Reactions." *Histochemistry*, (1985) 82(3):201–204.

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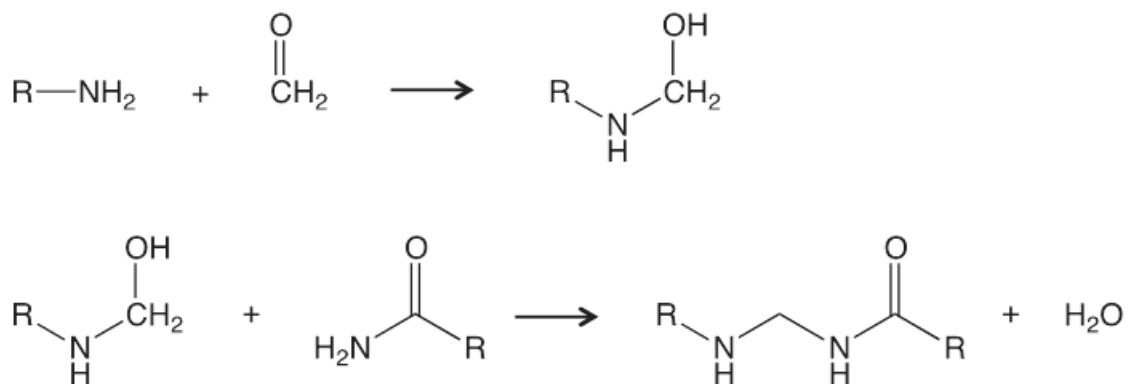


Figure 4. Simplified reaction schematic of proteins with formalin.

The resulting polymer has a much higher stiffness due to the newly formed chemical cross-links present. This increase in stiffness allows tissue samples to be sectioned by various techniques including microtoming.

## PROLENE

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Ethicon's antioxidant stabilized polypropylene-based resin is known by the tradename PROLENE. The resin was determined to be "safe and effective for use" in nonabsorbable surgical sutures by the FDA in 1969,<sup>15</sup> and has been used ever since. PROLENE sutures are manufactured by a melt spinning process (previously described in this report).<sup>16</sup> In addition to sutures, Ethicon has knit PROLENE filaments in to mesh materials used in hernia repair and to treat pelvic organ prolapse.

### Composition

As with many commercially available resin compounds, Ethicon's PROLENE resin is comprised of several raw materials ingredients in addition to the base isotactic polypropylene. The additional formulation ingredients and corresponding loading level ranges are<sup>17</sup>:

- Calcium Stearate – 0.25-0.35% - lubricant to help reduce tissue drag and promote tissue passage
- Santonox R – 0.10-0.30% –primary hindered phenol antioxidant
- Dilauralthiodipropionate (DLTDP) – 0.40-0.60% - secondary thioester antioxidant
- Procol LA-10 – 0.25-0.35% – lubricant to help reduce tissue drag and promote tissue passage
- Copper Phthalocyanate (CPC) Pigment – 0.55% max – colorant to enhance visibility (in blue filaments only)

A summary of the full resin history including information on compounding, manufacturing, and formulation changes can be found in Karl's memo entitled "PROLENE Resin Manufacturing Specifications".<sup>17</sup>

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<sup>15</sup> NDA – 4.16.1969 PROLENE FDA Approval (ETH.MESH.09625731-09625737).

<sup>16</sup> FDA – Reclassification.pdf (ETH.MESH.10665538 – 10665565).

<sup>17</sup> John Karl's January 23, 2003 Memo titled PROLENE Resin Manufacturing Specifications (Eth.Mesh.02268619 – 02268621).

## PROLENE Biocompatibility

The U.S. Food and Drug Administration (FDA) stipulates that a medical device “should not, either directly or through the release of their material constituents: (i) produce adverse local or systemic effects; (ii) be carcinogenic; or, (iii) produce adverse reproductive and developmental effects.”<sup>18</sup> The device manufacturer must follow FDA guidelines and evaluate material biocompatibility with certain tests that can vary depending on factors such as the intended application (e.g., duration and location of patient contact); alternatively, a manufacturer may not need to conduct all biocompatibility tests if its device is composed of materials that have been well characterized physically and chemically and have a long history of safe use.<sup>18</sup> The protocols for these tests are contained in standards established by the U.S. Pharmacopeia (USP), the International Organization for Standardization (ISO), and ASTM International.<sup>19</sup>

Prior to the FDA’s approval of PROLENE sutures in 1969,<sup>15</sup> Ethicon performed multiple animal implant studies to determine PROLENE’s effect *in vivo*. These studies, performed on rats, dogs, and rabbits,<sup>20</sup> primarily investigated the tissue reactions caused by both colored and colorless sutures implanted in animal hosts. It was found that, the “polypropylene suture was well tolerated by tissue, evoked a reaction of the type associated with relatively non-irritation (sic) foreign bodies, was not absorbed during the test periods, did not lose appreciable tensile strength, and was not carcinogenic.”

As mentioned previously, in 1969 the FDA approved PROLENE sutures as a “new drug,” stating that “We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling.”<sup>15</sup> Later, in 1990 the Center for Devices and Radiological Health (CDRH) of the FDA reclassified nonabsorbable polypropylene surgical sutures from class III to class II<sup>16</sup> stating that “it is apparent to the FDA that a class III designation for nonabsorbable polypropylene surgical suture

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<sup>18</sup> FDA Guidelines on Premarket Approval of Medical Devices, accessed July 25, 2015, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050490.htm#bio>.

<sup>19</sup> FDA Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, accessed July 25, 2015, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm>.

<sup>20</sup> PROLENE suture NDA Preclinical Studies.pdf (ETH.MESH.09626242 – 09626359).

constitutes overregulation.” The FDA class II designation is used for devices for which general controls are insufficient to “assure a device’s safety and effectiveness” but “sufficient information exists to establish a performance standard to provide such an assurance.”<sup>16</sup> The FDA concluded that the development of the performance standard necessary for class II devices was of low priority.<sup>16</sup>

In addition to conducting animal studies to analyze PROLENE sutures, Ethicon also performed studies on rabbits<sup>21</sup> and rats<sup>22</sup> to analyze the tissue reaction to implanted meshes comprised of knitted PROLENE filaments. These studies showed that “The tissue reaction to TVT mesh was characterized by generally mild chronic inflammation during the 28-day [rat] study, which was comparable to the tissue reaction observed for PROLENE polypropylene mesh” and that “The reactions to PROLENE mesh were similar in type and extent to the response elicited by Marlex mesh implanted as a control” in the rabbit study, further supporting PROLENE’s biocompatibility.

In order for PROLENE mesh to be used as a permanent tissue implant, Ethicon must comply with ISO 10993<sup>23</sup> and analyze the cytotoxicity, sensitization, and genotoxicity, among other tests, of the PROLENE mesh.<sup>24</sup> The safety of PROLENE meshes has been demonstrated through a long history of clinical use of PROLENE sutures, as well as confirmatory cytotoxicity tests. Because of the historical clinical safety of PROLENE sutures, no additional in-depth testing was considered necessary as all of the relevant biological effects listed in ISO 10993 had been previously investigated.<sup>23</sup>

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<sup>21</sup> 1973 Rabbit Study for PROLENE Mesh.pdf (ETH.MESH.10575607 – 10575613).

<sup>22</sup> PSE 97-0197.pdf (ETH.MESH.05315240 – 05315295).

<sup>23</sup> Eth Mesh 04384112 – Biocompatibility Risk Assessment for the TVT-L Device – June 6 2001.pdf (ETH.MESH.04384112 – 04284125).

<sup>24</sup> ISO 10993-1-2009.pdf.

## Mesh as a Medical Device

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### Introduction to Surgical Mesh

Surgical meshes are typically implanted in the body for the repair of soft tissues, including abdominal wall defects (hernias), uro-gynecological anatomy, and cardio-thoracic defects.<sup>25</sup>

The design and composition of surgical mesh has evolved significantly over time. The first examples were introduced in the early 20<sup>th</sup> century, and were composed of metals like silver, tantalum, and stainless steel. All were discontinued due to complications, including corrosion, metal fragmentation, erosion, and infection.<sup>25</sup> Polymeric mesh materials date back to the 1930s, when polypropylene mesh was first used to treat abdominal hernias.<sup>27</sup>

Due to its decades-long success in the field of hernia management, surgical mesh has also become prevalent in the treatment of urological and gynecological conditions, such as urinary incontinence and pelvic organ prolapse. The underlying principle behind these interventions is simple: mesh structures comprised of biocompatible materials are used to reinforce existing tissue, providing both anatomic and functional results.<sup>26</sup>

### Current Surgical Mesh Materials

The pelvic organs, which include the bladder, urethra, uterus, vagina, perineal body, and rectum, are maintained in position via the pelvis and a network of muscles and connective tissues. Pelvic organ prolapse is a condition characterized by the downward displacement of some or all pelvic organs, sometimes resulting in a bulge within the vagina. Lack of support for the urethra can also lead to stress urinary incontinence.<sup>27</sup>

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<sup>25</sup> Pandit, A. S., Henry, J. A. "Design of Surgical Meshes – an Engineering Perspective." *Technol. Health Care*, (2004) 12(1):51–65.

<sup>26</sup> Dällenbach, P. "To Mesh or Not to Mesh: A Review of Pelvic Organ Reconstructive Surgery." *Int. J. Womens Health*, (2015) 331.

<sup>27</sup> Kanagarajah, P., Ayyathurai, R., Gomez, C. "Evaluation of Current Synthetic Mesh Materials in Pelvic Organ Prolapse Repair." *Curr. Urol. Rep.*, (2012) 13(3):240–246.

The use of surgical mesh for female pelvic surgery dates back to the 1930s and 1950s, when nylon (polyamide) and Mersilene® (polyethylene terephthalate) were investigated as potential biomaterials for urinary incontinence surgery, respectively.<sup>27,28,29</sup> Today, surgical mesh used in pelvic organ prolapse repair is predominantly manufactured from monofilament polypropylene in various weights and pore sizes.<sup>30</sup> The first FDA-approved synthetic mesh manufactured specifically to treat urinary incontinence was produced by Island Biosurgical, Inc., which was demonstrated to be substantially equivalent to Marlex® polypropylene in 1996.<sup>26,31</sup> That same year, Ethicon obtained approval to market modified PROLENE, a mesh constructed of knitted filaments of extruded polypropylene, for repair of “hernia and other fascial deficiencies”.<sup>32</sup>

One of the earliest FDA-approved polypropylene-based products for female pelvic reconstructive surgery was Gynemesh® (Ethicon).<sup>26,33</sup> Since then, several medical device manufacturers have obtained approval to market polypropylene meshes for similar use, including C.R. Bard,<sup>34</sup> American Medical Systems,<sup>35</sup> Mpathy Medical Devices,<sup>36</sup> Sofradim,<sup>37</sup> and Coloplast.<sup>38</sup> Mesh products are also marketed as kits that include not only a precut mesh, but also tools to aid its implantation. Manufacturers of polypropylene-based mesh kits include C.R. Bard,<sup>39</sup> American Medical Systems,<sup>40</sup> Mentor,<sup>41</sup> MLE,<sup>42</sup> and Boston Scientific.<sup>43,44</sup>

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<sup>28</sup> Birch, C. “The Use of Prosthetics in Pelvic Reconstructive Surgery.” *Best Pract. Res. Clin. Obstet. Gynaecol.*, (2005) 19(6):979–991.

<sup>29</sup> DeBord, J. R. “Prostheses in Hernia Surgery: A Century of Evolution.” *Abdominal Wall Hernias*. Ed. Robert Bendavid, Jack Abrahamson, Maurice E. Arregui, Jean Bernard Flament, et al. New York, NY: Springer New York, 2001. 16–32.

<sup>30</sup> Edwards, S. L., Werkmeister, J. A., Rosamilia, A., Ramshaw, J. A. M., et al. “Characterisation of Clinical and Newly Fabricated Meshes for Pelvic Organ Prolapse Repair.” *J. Mech. Behav. Biomed. Mater.*, (2013) 2353–61.

<sup>31</sup> Island Biosurgical, Inc. Island Biosurgical Bolster. 510(k) #K960101.

<sup>32</sup> Ethicon, Inc. Modified PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh. 510(k) #962530.

<sup>33</sup> Ethicon, Inc. Gynemesh PROLENE Soft (Polypropylene) Mesh. 510(k) # K013718

<sup>34</sup> C.R. Bard, Inc. Avaulta™ Solo Support System and Avaulta™ Plus Biosynthetic Support System. 510(k) #K063712.

<sup>35</sup> American Medical Systems. AMS Large Pore Polypropylene mesh. 510(k) #K033636.

<sup>36</sup> Mpathy Medical Devices, Ltd. Minimesh® polypropylene mesh. 510(k) #K041632.

<sup>37</sup> Sofradim Production. Parietene™ Duo Polypropylene mesh and Parietene™ Quadra Polypropylene mesh. 510(k) #K072951.

<sup>38</sup> Coloplast A/S. Restorelle™ polypropylene mesh. 510(k) #K103568.

<sup>39</sup> C.R. Bard, Inc. Bard® InnerLace™ BioUrethral Support System. 510(k) #K031295.

## Suture and Mesh Literature Review

As part of its analysis, Exponent has considered peer-reviewed literature that investigated the use of polypropylene sutures and mesh as medical implants. Our account and summary points of these literature papers are given below.

### Clavé

Clavé<sup>45</sup> studied 100 explanted mesh samples that were removed due to complications. After explantation, samples were rinsed and placed in a 4% neutral buffer formalin solution. After storage in the formalin solution, samples for Fourier transform infrared spectroscopy (FTIR) were washed in a NaOCl solution for 26 hours, washed with deionized water, and then extracted with pure cyclohexane for 24 hours at room temp. Clavé did not verify that the cleaning protocol entirely removed biological material from the mesh, stating that, “FTIR absorption bands between 1,615 and 1,650  $\text{cm}^{-1}$  could be attributed either to carboxylate carbonyl or to residual products of biological origin.” Clavé further states, “FTIR analysis neither confirmed nor excluded oxidation of PP in the *in vivo* environment.”

While the use of FTIR can be very beneficial in the field of polymer science, it is important to understand the limitations. One such limitation is the precision of the sampling volume. The penetration depth of the infrared (IR) beam into the sample is typically 0.5  $\mu\text{m}$  to 5  $\mu\text{m}$ , depending on experimental conditions such as the wavelength of light and the angle of incidence.<sup>46</sup> According to Ethicon documents, the depth of microcracks in explanted PROLENE sutures has been measured to be 0.5 – 4.5  $\mu\text{m}$ .<sup>47</sup> Furthermore, the spot size for sampling may

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<sup>40</sup> American Medical Systems. BioArc TO™ Subfascial Hammock. 510(k) #K040538.

<sup>41</sup> MentorCorp. Mentor ObTape™ Trans-obdurator Surgical Kit. 510(k) #042851.

<sup>42</sup> MLE, Inc. Suture Fixation Device. 510(k) #K021834.

<sup>43</sup> Boston Scientific Corp. Pinnacle Pelvic Floor Repair Kit II. 510(k) #081048.

<sup>44</sup> Boston Scientific Corp. Pinnacle Lite Pelvic Floor Repair Kit. 510(k) #122459.

<sup>45</sup> Clavé, A., Yahi, H., Hammou, J.-C., Montanari, S., et al. “Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants.” *Int. Urogynecology J.*, (2010) 21(3):261–270.

<sup>46</sup> ATR – Theory and Applications.pdf Pike Technologies.

<sup>47</sup> “Crack Depth in Explanted PROLENE Polypropylene Sutures memo (ETH.MESH.123831405 – 123831406).

range from several millimeters down to 15  $\mu\text{m}$ , depending on microscope attachment.<sup>48</sup>

Therefore a given FTIR spectrum may consist of functional groups from neighboring materials and the underlying bulk fiber material.

Clavé also analyzed both pristine exemplar mesh and explanted polypropylene mesh materials by differential scanning calorimetry (DSC). DSC is an analysis technique used to evaluate the thermal properties of materials such as glass transition temperature, melting point and heat of fusion. His study concluded that, “no difference between DSC thermograms of pristine and degraded samples was found.”

Clavé’s only claimed evidence of “degradation” is the presence of a cracked outer layer on the explants, which was imaged via scanning electron microscopy (SEM). However, Clavé failed to fully remove the biologic material from these samples as evidenced by the intact tissue present in the SEM images and neglected to analyze or to chemically identify the observed cracked layer. Unlike the samples that underwent FTIR that were cleaned with NaOCl, the samples that were analyzed by SEM did not undergo any cleaning prior to imaging. Instead, the samples were fixed in formalin, and then further fixed and preserved with 1% glutaraldehyde and post fixed with a 1% osmium tetroxide solution. Finally, these samples were dehydrated with a series of ethanol solutions and dried using hexamethyldisilazane before being coated with gold-palladium. In short, Clavé presumes the cracked outer layer to be evidence of “degradation”, however, neither generated any data that identified the chemical composition of the outermost layer nor conclusively determined whether there was any evidence of polypropylene degradation, including oxidation.

## De Tayrac

A separate paper by de Tayrac et al. investigated Clavé’s conclusion regarding a correlation between infection and polypropylene “degradation.” In this study, de Tayrac *et al.* implanted polypropylene mesh materials (unspecified manufacturer) into Wistar rats along with *E. coli*

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<sup>48</sup> EAG FTIR Technique Note.

bacteria for 30 days.<sup>49</sup> After the mesh was harvested, it was not formalin fixed, but rather it was washed in a solvent, dimethyl sulfoxide (DMSO), and ultrasonically shocked. SEM images of these samples prior to ultrasonic shock treatment showed evidence of transverse cracking, but after the ultrasonic treatment the mesh filaments appeared smooth with no persisting microscopic evidence of a cracked outer layer. Unlike Clavé et al., de Tayrac concluded that the originally observed transverse cracking “appeared to concern only the biofilm, with no effect on the implant thread itself.”

## Costello

To evaluate the physiochemical changes that are indicative of oxidation allegedly associated with polypropylene *in vivo*, Costello *et al.* analyzed fourteen explanted polypropylene/expanded polytetrafluoroethylene composite hernia meshes.<sup>50</sup> These composite hernia meshes were not manufactured by Ethicon, none were comprised of PROLENE, and had different knit structures and pore sizes, i.e., the multi-polymer meshes analyzed were inherently different from Ethicon’s PROLENE mesh and therefore the conclusions reached in this study are not directly applicable to PROLENE mesh material or design.

In this study, Costello preserved and stored the explanted meshes in a 10% v/v formalin solution before the tissue surrounding the mesh was removed in a NaOCl bath at 37 °C for 2 hrs. Costello did not perform any analysis to verify the extent to which the cleaning procedure removed bulk tissue and other biological residues from the mesh surface.

Through SEM examination, Costello observed “cracks, fissures, and increased surface roughness,” as well as peeling on the surface of the explanted samples, which can be explained by the presence of buildup of foreign material on the exterior of the mesh filaments. Costello failed to perform any type of chemical characterization on this outer “peeling” material and, therefore, the chemical composition of this layer was simply undetermined in the study. Using differential scanning calorimetry (DSC) techniques, Costello claimed that a decrease in melting

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<sup>49</sup> De Tayrac, R., Letouzey, V. “Basic Science and Clinical Aspects of Mesh Infection in Pelvic Floor Reconstructive Surgery.” *Int. Urogynecology J.*, (2011) 22(7):775–780.

<sup>50</sup> Costello, C. R., Bachman, S. L., Ramshaw, B. J., Grant, S. A. “Materials Characterization of Explanted Polypropylene Hernia Meshes.” *J. Biomed. Mater. Res. B Appl. Biomater.*, (2007) 83B(1):44–49.

point was observed in the explanted samples when compared to the exemplar mesh material. Melt temperature suppression could be explained in many ways. For example, the mesh material has the potential to undergo plasticization *in vivo* as seen in a study performed by Ethicon on PROLENE sutures explanted from dogs.<sup>51</sup> This study found that after seven years *in vivo*, PROLENE sutures showed an increase in elongation at break and a decrease in modulus, which are consistent with plasticization.

Through a compliance test measuring the work required to “bend the mesh in half and push it through a 2.92 cm<sup>2</sup> slot.” Costello claimed to demonstrate a decrease in compliance of the explanted mesh. Costello alleged that this decrease in compliance “is evidence of oxidation,”<sup>50</sup> but failed to take into account the “permanent deformation of the material while *in vivo*,”<sup>50</sup> which is a result of the natural stress relaxation of the polymer. The folded geometry will artificially alter the apparent compliance (stiffness/rigidity) of the mesh. The flexural rigidity of a material is directly proportional to the modulus of elasticity and the moment of inertia, which is a geometrical term based on specimen geometry.<sup>52</sup> The “permanent deformation” of the explanted mesh makes a direct comparison of the rigidity of the exemplar and explants more complicated due to different moments of inertia. To truly compare the explanted and exemplar mesh materials it is necessary to calculate the modulus of elasticity, which is independent of specimen geometry. Costello also reports that the total work required to bend the mesh and push it through the slot is greater for explanted mesh materials than for an exemplar mesh. This is another example of Costello’s lack of fundamental understanding of the importance of specimen geometry in mechanical testing. The work required to bend a sample is related to its stiffness, which as discussed above is a function of both the material’s modulus *and* specimen geometry. Thus the increase in total work observed in this test is most likely due to the folded specimen geometry, not oxidation or degradation. Furthermore, Costello’s claim of a decrease in compliance (increase in stiffness/rigidity) is contrary to the results of the seven year dog study performed by Ethicon’s scientists.<sup>51</sup> This study found that after seven years *in vivo*, PROLENE sutures decreased in stiffness (increase in compliance) as evidenced by a reduction in modulus of PROLENE sutures after seven years *in vivo*.

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<sup>51</sup> Ethicon’s Seven Year Dog Study

<sup>52</sup> Lubliner, J., Papadopoulos, P. *Introduction to Solid Mechanics: An Integrated Approach*. New York, NY: Springer, 2014.

Costello *et al.* also “most likely” attributed the broadening of the melting point observed in the explanted samples to *in vivo* oxidation. Their rationale is that oxidized polypropylene will result in an increase in polydispersity, which would correlate to a broader observed melting point. However, the degree to which this broadening occurred was not reported, and as such is difficult to analyze. Melting point broadening could also be due to variability in the concentration of low molecular weight species that may have been absorbed by the material while *in vivo*. Additionally, unexplained endothermic and exothermic peaks are seen in the DSC data at 230°C in the exemplar curve (Composix E/X), 275°C, 320°C and 340°C in the Subject #2 curve, and 335°C in the Subject #9 curve, which are on the order of the melting point transition, thus rendering any perceived small change in the broadening of the melting point unfounded.

Finally, Costello stated that “Oxidized materials are expected to undergo some degree of weight loss as the material is degraded by the body. Thus oxidized materials should have less weight available to be lost during TGA.” This statement shows a fundamental misunderstanding of TGA analysis. Typically, TGA data are used to report the onset of degradation or the residual (often inorganic) mass at the end of the test. Data is reported as a *percentage* of the original weight of the sample placed in the sample chamber. Assuming homogeneous mixing of any inorganic compounds within a polymer sample, the degree of weight loss determined by TGA will be the same regardless of whether or not the polymer has experienced oxidation. In the absence of any inorganic filler, 100% weight loss of the sample is expected if the TGA analysis is carried through to completion. Furthermore, Costello’s data shows a shift to higher temperatures in the peak of the derivative of the mass loss with temperature curve for explanted samples (Subject #2 and Subject #9). This demonstrates the exemplar mesh degrades at a higher rate at lower temperatures than the explanted mesh materials, which challenges, if not contradicts, Costello’s hypothesis of oxidation.

## Cozad

To understand tissue-material interactions occurring *in vivo*, Cozad *et al.* examined 11 explanted composite hernia meshes (not PROLENE, and not manufactured by Ethicon) that contained

polypropylene and expanded polytetrafluoroethylene (ePTFE) components.<sup>53</sup> These composite meshes analysis, authors, and methodology were very similar to the work previously outlined by Costello,<sup>50</sup> and will not be repeated again in complete detail. Cozad, like Costello, performed analysis (FTIR, DSC, TGA and SEM imaging) on explanted mesh materials without verifying that the samples were fully cleaned. In fact, the researchers readily admit to choosing sections to analyze which were “the most ‘pristine-like’ sites with no apparent tissue adsorption” strongly suggesting that they were aware that the overall samples were not adequately cleaned. Furthermore, Cozad attributes an increase in FTIR absorbance peaks at  $2850\text{ cm}^{-1}$  to “surface hydrocarbon formation” again suggesting that the explanted mesh was not fully cleaned before analysis was performed. But instead of developing a more thorough cleaning procedure, Cozad *et al.* simply continued with their analysis without any apparent concern for the possibility of inaccurate results and without considering that the observed crust may be biologic in nature. The authors state the polypropylene portions of the mesh oxidized, while the ePTFE portions cross-linked *in vivo*. One of the major sources for this conclusion is the FTIR data that shows a nearly identical peak seen at  $1730\text{ cm}^{-1}$  in both the explanted polypropylene and ePTFE. The likelihood that crosslinking in ePTFE and oxidation in polypropylene showing a nearly identical peak (they are extremely similar in shape and location) is unlikely. Further, the authors give no plausible reason the ePTFE could crosslink *in vivo* as most studies, some of which are referenced in the Cozad article, require irradiation or high temperature and vacuum to crosslink PTFE.<sup>54,55,56</sup> Rather, a more likely scenario is that the  $1730\text{ cm}^{-1}$  peak observed is actually an artifact or residue of sample handling such as adhesive used in electron microscopy. Adhesive acrylate peaks look strikingly similar to the  $1730\text{ cm}^{-1}$  peaks reported by Cozad *et al.*

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<sup>53</sup> Cozad, M. J., Grant, D. A., Bachman, S. L., Grant, D. N., et al. “Materials Characterization of Explanted Polypropylene, Polyethylene Terephthalate, and Expanded Polytetrafluoroethylene Composites: Spectral and Thermal Analysis.” *J. Biomed. Mater. Res. B Appl. Biomater.*, (2010) 455–462.

<sup>54</sup> Lappan, U., Geißler, U., Lunkwitz, K. “Changes in the Chemical Structure of Polytetrafluoroethylene Induced by Electron Beam Irradiation in the Molten State.” *Radiat. Phys. Chem.*, (2000) 59(3):317–322.

<sup>55</sup> Pugmire, D. L., Wetteland, C. J., Duncan, W. S., Lakis, R. E., et al. “Cross-Linking of Polytetrafluoroethylene during Room-Temperature Irradiation.” *Polym. Degrad. Stab.*, (2009) 94(9):1533–1541.

<sup>56</sup> Lappan, U., Geißler, U., Häußler, L., Jehnichen, D., et al. “Radiation-Induced Branching and Crosslinking of Poly(tetrafluoroethylene) (PTFE).” *Nucl. Instrum. Methods Phys. Res. Sect. B Beam Interact. Mater. At.*, (2001) 185(1-4):178–183.

## Liebert

Liebert *et al.*<sup>57</sup> implanted polypropylene sutures with and without antioxidants (neither of which were PROLENE) into the backs of hamsters. They describe evidence of oxidation in the sutures without antioxidants, but claim to see no evidence of oxidation in sutures with antioxidants after 108 days of implantation. Liebert *et al.* tracked degradation by monitoring carbonyl content via FTIR, molecular weight by gel permeation chromatography (GPC) and  $\tan \delta$  by dynamic mechanical analysis (DMA) and found no change in the filaments with antioxidant. They conclude that the oxidation process “is retarded effectively by using an antioxidant.” This finding is in concert with the historical use of antioxidant stabilizers in polypropylene formulations that are used as implantable materials.

## Mary

Comparison of PVDF (Teflene, Péters Laboratoire Pharmaceutique) and polypropylene (PROLENE, Ethicon) sutures implanted in female dogs for periods of time ranging from 4 hours to 2 years were studied by Mary *et al.*<sup>58</sup> Explanted samples examined via SEM and FTIR were cleaned with an enzyme incubation technique, rinsed in buffer and deionized water solutions and dried. Comparative FTIR spectra for PVDF and polypropylene enzymatically cleaned explants were tracked with time, only presenting the absorbance data at  $1740\text{ cm}^{-1}$ , the peak assigned to carbonyl stretching. In all samples tested, Mary reported a rapid increase in carbonyl presence to a maximum value followed by a decrease and then stabilization. This decrease in carbonyl intensity which occurs at differing times for each sample shows absolutely no support for Mary’s theory of polypropylene *in vivo* degradation. There is no scientific basis for a claim of partial recovery of degradation as indicated by the reduction in carbonyl intensity. Instead, this data suggests that Mary was sampling a material other than the surface of the polypropylene filament such as biologic material which is changing with implantation time. The lack of testing to verify complete sample cleaning further supports this hypothesis. Alternatively, Mary may have been sampling locations where there was natural variation in the concentration of any

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<sup>57</sup> Liebert, T. C., Chartoff, R. P., Cosgrove, S. L., McCuskey, R. S. “Subcutaneous Implants of Polypropylene Filaments.” *J. Biomed. Mater. Res.*, (1976) 10(6):939–951.

<sup>58</sup> Mary, C., Marois, Y., King, M. W., Laroche, G., et al. “Comparison of the In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery.” *ASAIO J.*, (1998) 44(3):199–206.

carbonyl-containing molecules within the polymer matrix. Furthermore, microscopic examination of cleaned polypropylene samples showed an absence of cracking in both sample types at 6 months, the time at which the carbonyl signal in the FTIR had already begun to stabilize, suggesting a lack of correlation between reported carbonyl functionality and observed cracking.

## Wood

In order to try to separate out the effects of physiological variability between different patients, Wood *et al.* studied three explanted mesh samples from the same patient. The three different mesh samples were comprised of polypropylene, expanded polytetrafluoroethylene (ePTFE), and polyethylene terephthalate (PET) and were implanted to treat three separate ventral hernias.<sup>59</sup> The patient has a medical history of gout, morbid obesity, tobacco usage and sleep apnea. The authors did not state why there were different materials implanted in the same patient.

After explantation, all specimens were placed in a formalin solution followed by immersion in a NaOCl solution to remove residual tissue. After the cleaning procedure Wood *et al.* collected FTIR spectra of each of the explants and corresponding exemplar mesh materials to identify chemical changes on the surface of the mesh. FTIR revealed an increase in carbonyl functionality on each of the explanted specimens when compared to pristine exemplar meshes “which could indicate the presence of scar tissue and/or chemical degradation.” The presence of scar tissue on the cleaned specimens is further supported by photographs of the cleaned and explanted mesh which clearly show evidence of attached tissue and discoloration associated with incomplete cleaning. Additionally, the FTIR spectra of explanted ePTFE and PET show an unexplained increase of absorption bands at  $3100 - 2800\text{ cm}^{-1}$ , which have been attributed to C-H bond stretching.<sup>60</sup> This increase is unexpected<sup>61,62</sup> in the degradation of both polypropylene

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<sup>59</sup> Wood, A. J., Cozad, M. J., Grant, D. A., Ostdiek, A. M., et al. “Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient.” *J. Mater. Sci. Mater. Med.*, (2013) 24(4):1113–1122.

<sup>60</sup> Chen, Z., Hay, J. N., Jenkins, M. J. “FTIR Spectroscopic Analysis of Poly(ethylene Terephthalate) on Crystallization.” *Eur. Polym. J.*, (2012) 48(9):1586–1610.

<sup>61</sup> Fotopoulou, K. N., Karapanagioti, H. K. “Surface Properties of Beached Plastics.” *Environ. Sci. Pollut. Res.*, (2015) 22(14):11022–11032.

and ePTFE, which further indicates Wood's lack of sufficient cleaning. Wood goes on to evaluate the cleaned mesh materials using SEM microscopy and modulated differential scanning calorimetry, but does not provide evidence of further or complete cleaning. These results cannot be relied upon to provide conclusive evidence of degradation due to the presence of tissue and/or other contaminants.

## Guelcher

Guelcher has studied the *in vitro* oxidation of both polypropylene pellets without antioxidants and PROLENE mesh (with antioxidants).<sup>63</sup> The samples were placed in an H<sub>2</sub>O<sub>2</sub> solution containing 0.1 M CoCl<sub>2</sub> for up to five weeks. This solution was used previously by Zhao as one component of a regimen designed to mimic “the respiratory burst of adherent macrophages and foreign-body giant cells” on a poly(etherurethane) (PEU) elastomer.<sup>64</sup> In Zhao's study, the validation of this regimen on this particular polymer as a mimic to *in vivo* conditions was in part performed through SEM image comparison of explanted samples and *in vitro* samples. In short, the *in vitro* oxidizing environment established by Zhao was dependent on the polymer system being analyzed in the Zhao study, namely poly(etherurethane), not polypropylene. Guelcher uses a similar method to induce degradation in polypropylene; however, he never validated that his method was appropriate for polypropylene. In fact, as can be seen from Guelcher's one and only SEM image of PROLENE mesh after treatment in the H<sub>2</sub>O<sub>2</sub> solution for five weeks, it is evident that the “pitting and flaking” seen in these samples is completely inconsistent with the morphology of explanted polypropylene mesh samples, thus calling into question the validity of this method with polypropylene and demonstrating that Zhao's results for poly(etherurethane) cannot be extrapolated to polypropylene.

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<sup>62</sup> Atta, A., Fawzy, Y. H. A., Bek, A., Abdel-Hamid, H. M., et al. “Modulation of Structure, Morphology and Wettability of Polytetrafluoroethylene Surface by Low Energy Ion Beam Irradiation.” *Nucl. Instrum. Methods Phys. Res. Sect. B Beam Interact. Mater. At.*, (2013) 30046–53.

<sup>63</sup> Guelcher, S. A., Dunn, R. F. “Oxidative Degradation of Polypropylene Pelvic Mesh in Vitro.” *Int Urogynecol J*, (2015) 26(Suppl 1):S55–S56.

<sup>64</sup> Zhao, Q. H., McNally, A. K., Rubin, K. R., Renier, M., et al. “Human Plasma Macroglobulin Promotes *in Vitro* Oxidative Stress Cracking of Pellethane 2363-80A: *In Vivo* And *In Vitro* Correlations.” *J. Biomed. Mater. Res.*, (1993) 27(3):379–388.

## Artifacts in Microtome Processing

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Microtoming is a known method of preparing thin cross-sections of both biologic and synthetic materials.<sup>65</sup> The process of microtoming involves preparing a sample by embedding in paraffin or another stiff matrix, then making slices of varying thickness with a very sharp knife or blade. The process of microtoming is often used for the purpose of preparing very thin slices of cross-sections as part of a staining protocol in pathology applications to illuminate different types of cells and/or tissue that may be present within a sample. As discussed in my separate report regarding intentional oxidation of PROLENE, it is also a technique that has been used in polymer science for decades.

It is important to note that not every material can be prepared by microtoming. Often, samples that are too soft cannot be sectioned effectively, resulting in a poorly prepared material slice with extraneous artifacts, including edge imperfections, which are not representative of the pre-sectioned material sample. To avoid these artifacts, biological tissue samples are often fixed, which among other effects, hardens the tissue for microtoming.<sup>12</sup>

Likewise, heterogeneous samples with both hard and soft matter can be difficult to microtome without inducing artifacts. As an example, McInnes reports on artifacts caused by bone fragments in soft brain tissue. The hard fragments can be “moved by the microtome knife-edge during cutting and this causes shattering and distortion of the tissue section.”<sup>66</sup>

During the cutting process, if the microtome knife is set at too acute of an angle or if the knife is too dull, it can compress the tissue specimen as it is being cut. This effect is exacerbated when a particularly soft material is being sectioned. In this case, the microtome knife can compress the tissue specimens and result in streaks, cracks, waviness and other artifacts that run parallel to the

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<sup>65</sup> Bell, G. R. “Microtoming: An Emerging Tool for Analyzing Polymer Structures.” *Plastics Engineering*.

<sup>66</sup> McInnes, E. “Artefacts in Histopathology.” *Comp. Clin. Pathol.*, (2005) 13(3):100–108.

**Attorney Client Privilege—September 15, 2015**

edge of the microtome knife, and in some cases, rendering the sectioned tissue specimen unable to be adequately processed via microscope examination.<sup>66,67</sup>

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<sup>67</sup> Janzen, W., Ehrenstein, G. W. “Microtomy of Polymeric Materials Part 2: Application of Microtomy.” *Pract. Metallogr.*, (1989) 26549–558.

## Ethicon's Investigation

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In the course of its investigation, Exponent has reviewed a series of internal Ethicon documents detailing experiments conducted on explanted sutures in the 1980's.

### Microcrack Committee Investigation

Ethicon conducted experiments to investigate alleged cracking observed on the outer surface of explanted PROLENE sutures in the 1980s. As part of their internal investigation, Ethicon formed a "microcrack committee" of scientists that carried out multiple experiments including various forms of microscopy, mechanical testing, melting point analysis and FTIR analysis on both explanted materials and intentionally oxidized controls to understand the composition of the observed cracked layer on the outer surface of explanted PROLENE sutures. The studies performed by this committee contain test reports, internal Ethicon memos, and correspondence among Ethicon staff, scientists, and surgeons.

### Microscopy

Ethicon's scientists examined numerous uncleaned explanted PROLENE sutures by both optical microscopy<sup>68,69,70,71,72</sup> and SEM<sup>47,71,72</sup>, confirming an outer cracked layer on some of the explants. Further microscopic examination was performed using cross-polarized light microscopy to determine if exemplar PROLENE sutures exhibited a core/shell morphology associated with variations in crystallinity resulting from the manufacturing process. It was found that there was "no indication of a gross skin feature on PROLENE sutures".<sup>71</sup>

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<sup>68</sup> 14 – "Examination of 5/0 and 6/0 Cardiovascular PROLENE Sutures Explanted after 2 to 6 Years Implantation" memo 1983.03.25 (ETH.MESH.15958410-58432)

<sup>69</sup> 15 – "Human Retrieval Specimens from Dr. Roger Gregory, Norfolk Surgical Group" memo 1983.03.29 (ETH.MESH.15955440-15955442)

<sup>70</sup> 19 – "Examination of PROLENE (Polypropylene) Sutures from Human Cardiovascular Explants" memo 1984.05.02 (ETH.MESH.15955462-15955468)

<sup>71</sup> 23 – "PROLENE Microcracking" memo 1984.11.05 (ETH.MESH.15958452-15958469)

<sup>72</sup> 24 – "PROLENE Polypropylene Suture Explant from Dr. Drewes" memo 1984.11.07 (ETH.MESH.15958405-15958407)

Using transmission electron microscopy (TEM) in diffraction mode<sup>71</sup> to examine an explanted cross-section further confirmed the presence of a semi-crystalline inner core material, and an *amorphous* cracked outer layer, suggesting the cracked outer layer was not PROLENE.

## Mechanical Testing

Tensile testing was performed by Ethicon's scientists on explanted PROLENE sutures of various sizes that were "relatively free from instrument damage"<sup>69</sup> and compared with exemplar sutures of similar sizes to determine the change in breaking strength. Explanted sutures exhibited breaking strengths ranging from 47%-110%<sup>73</sup> of the values obtained for their representative control sutures.<sup>69,70</sup> The elongation at break and modulus were not reported in this study and therefore it is impossible to determine if the reported reduction in breaking strength is a result of material degradation, or simply an *in vivo* plasticization effect as seen in seven year dog study, which will be discussed in detail later.<sup>51</sup>

## Melting Point Analysis

In a further effort to identify the composition of the cracked outer film on explanted PROLENE sutures, Ethicon investigated the melting point of the exterior layers. Explanted sutures were heated, resulting in contraction and peeling of the outer cracked surface layer. The suture and peeled layer were further heated until the bulk PROLENE suture had melted (~165°C). In most cases, the bulk fiber melted first "but the crack (sic) layer maintains its form,"<sup>71</sup> indicating that the cracked layer is not degraded PROLENE, which would have a *lower* melting temperature than bulk PROLENE. Ethicon repeated these melting point experiments with protein serum coated exemplar sutures with analogous results, stating that this "protein layer has similar characteristics to the crack layer on explants in that it separates from the fiber cleanly with heating and maintains its form after the PROLENE fiber has melted."<sup>71</sup>

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<sup>73</sup> Of the 13 sutures tested, 12 exhibited breaking strengths 75% or higher of values obtained for their representative control sutures.

## FTIR Analysis

FTIR is a technique used to identify particular chemical bonds present in a sample and to identify specific polymer types. Ethicon performed FTIR analysis of the cracked outer layer, bulk explanted sutures, intentionally oxidized controls, protein immersed controls, and exemplar PROLENE sutures to determine the composition of the cracked outer layer by the functional groups present in each type of sample.<sup>71,74,75</sup> As discussed previously, carbonyl containing functional groups are formed upon oxidation of polypropylene and are typically associated with absorption peaks between approximately  $1650\text{ cm}^{-1}$  and  $1810\text{ cm}^{-1}$  in the IR spectrum.<sup>8,76,77</sup> Interpreting the FTIR spectra obtained by Ethicon is non-trivial due to a multitude of factors. Characteristic functional groups in proteins,<sup>74</sup> DLTDP (antioxidant),<sup>75</sup> formaldehyde crosslinked proteins,<sup>14</sup> fatty acid esters,<sup>78</sup> and oxidized polypropylene<sup>75</sup> (Figure 5) include carbonyl groups, which confounds the interpretation of IR spectra generated from explanted meshes and sutures manufactured from PROLENE..

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<sup>74</sup> 25 – “Fourier Transform-Infrared Examination of PROLENE Microcrack and Photo-Oxidized Polypropylene” memo 1984.11.13 (ETH.MESH.15958336-15958395)

<sup>75</sup> 28 – “IR Microscopy of Explanted PROLENE Received from Prof. R. Guidoin” memo 1987.09.30 (ETH.MESH.12831391-12831404)

<sup>76</sup> Carlsson, D. J., Wiles, D. M. The Photodegradation of Polypropylene Films. III. Photolysis of Polypropylene Hydroperoxides. *Macromolecules*, (1969) 2(6):597–606.

<sup>77</sup> George, G. A., Celina, M., Vassallo, A. M., Cole-Clarke, P. A. Real-Time Analysis of the Thermal Oxidation of Polyolefins by FT-IR Emission. *Polym. Degrad. Stab.*, (1995) 48(2):199–210.

<sup>78</sup> Movasaghi, Z., Rehman, S., ur Rehman, D. I. “Fourier Transform Infrared (FTIR) Spectroscopy of Biological Tissues.” *Appl. Spectrosc. Rev.*, (2008) 43(2):134–179.

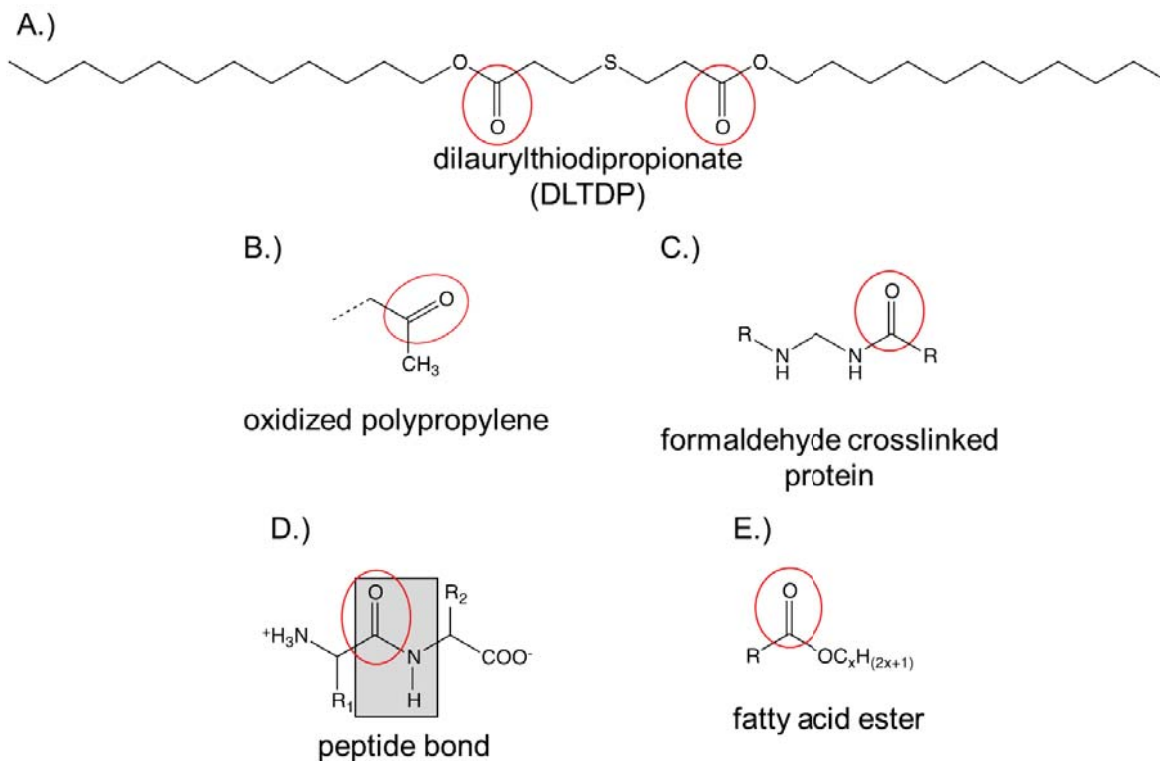


Figure 5. Chemical structure of dilaurylthiodipropionate<sup>79</sup> A.), oxidized polypropylene<sup>1</sup> B.), formaldehyde crosslinked proteins<sup>14</sup> C.), a peptide bond, which make up proteins<sup>80</sup> D.) and a fatty acid ester<sup>78</sup> E.). All of these molecules have functional groups which contain carbonyls (circled in red).

Ethicon performed studies that included FTIR spectroscopy of intentionally oxidized polypropylene and PROLENE samples that were immersed in protein serum.<sup>74</sup> Studies involving intentional oxidation, such as the hot pressed samples and the photo-oxidized induced samples, showed consistent carbonyl peaks in the 1720 cm<sup>-1</sup> region. Explanted samples and those immersed in protein serum inconsistently showed peaks in the 1700 cm<sup>-1</sup> to 1740 cm<sup>-1</sup> region, indicating oxidation was unlikely to be the contributing factor the peaks. Rather, carbonyl or other oxygen containing groups from the serum or *in vivo* conditions contributed to the observed peaks.

<sup>79</sup> Chemical Book, accessed August 23, 2015.

[http://www.chemicalbook.com/ChemicalProductProperty\\_EN\\_CB3712869.htm](http://www.chemicalbook.com/ChemicalProductProperty_EN_CB3712869.htm)

<sup>80</sup> Godbey, W. T. *An Introduction to Biotechnology the Science, Technology and Medical Applications*. Woodhead Publishing, 2014.

## Seven Year Dog Study

### Study Protocol

As part of the microcrack committee, Ethicon initiated a comprehensive 10-year *in vivo* study commencing in 1985. One of the primary motivations of this study was to assess the long-term effects, if any, of implantation on various suture materials. Ethicon selected PROLENE (polypropylene), PVDF (polyvinylidene fluoride), ETHILON (nylon 6 and nylon 6,6), and Novafil (polybutester) monofilament 5-0 sutures to be examined in this study. Periodic evaluations were performed after two, five, and seven years *in vivo*, with baseline testing of unimplanted sutures also performed at each period. Each periodic evaluation consisted of generating mechanical and chemical property data as well as surface morphology micrographs to capture any physical changes in the candidate suture materials. In this study, twenty-four mature female Beagle dogs served as animal models (five animals per study period, plus four replacements in case of premature death) Each animal had sutures implanted in six different locations, and each implant location received a bundle of six sutures (with each bundle containing a single type of suture) A simplified schematic of the surgery sites is shown in Figure 6.

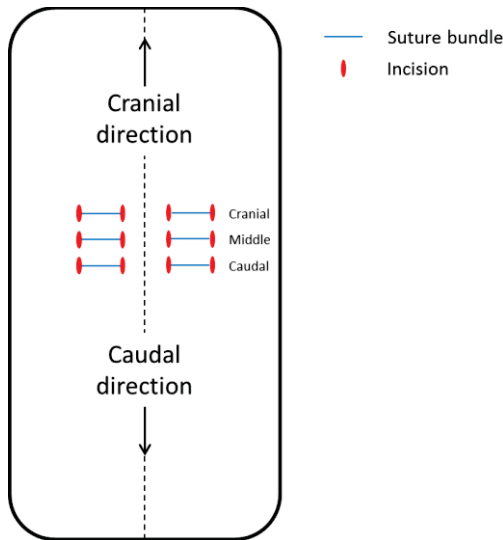


Figure 6. Simplified illustration of the ventral area of a dog torso, showing the location of the six suture implantation sites.

Five dogs were euthanized at each study period. For each suture type, one strand (selected at random) was immediately placed, without cleaning or being allowed to dry, into a test tube filled with sterilized deionized water to be examined and imaged with optical (OM), scanning electron (SEM), and infrared (IR) microscopy

The remaining five strands were examined for surface damage, and then placed into saline-soaked towels in preparation for tensile testing, which was performed on the explanted strands of each suture type and ten non-implanted exemplars. After testing, the chemical groups present on the surfaces of the fragments were identified by FTIR, and the molecular weight was evaluated by inherent viscosity, and gel permeation chromatography (GPC).

## Study Results

In this study, prior to additional testing and examination, FTIR spectra were taken on all explanted sutures to verify that they had been correctly identified during the explantation procedure.<sup>81</sup>

<sup>81</sup> Ethicon's Seven Year Dog Study (ETH.MESH.09888187) pg.115

IR microscopy is a technique very similar to FTIR, albeit with smaller spatial resolution. This technique made it possible to compare the chemical groups present in cracked and non-cracked regions. After seven years *in vivo*, spectra for PROLENE sutures showed “a broadened weak absorbance at about  $1650\text{ cm}^{-1}$ ,” Ethicon’s scientists concluded that this was “possible evidence of slight oxidation.”<sup>81</sup> The absorbance peak typically assigned to carbonyl containing functional groups in oxidized polypropylene is  $1650\text{-}1810\text{ cm}^{-1}$ .<sup>8,76,77</sup> However, it is important to note that these samples were not cleaned, in fact tissue was still present on the surface of the suture and “cracking of the suture was seen through the tissue.”<sup>82</sup> The existence of tissue, including tissue that may contain lipids or fatty acids, could readily account for the observed carbonyl functionality on the cracked surface of the suture; therefore no scientific conclusions can be drawn by IR microscopy regarding the oxidation of PROLENE sutures. The spectra from cracked areas on ETHILON and Novafil sutures were not different than spectra obtained from uncracked areas. However, it was noted that absorbance frequencies related to oxidation “would be masked by the strong carbonyl absorbances normally observed for these sutures.”<sup>81</sup> Thus, no conclusions could be drawn from the IR microscopy of any of the examined explanted sutures.

Direct molecular weight measurements via GPC were performed on both unimplanted controls and PROLENE sutures after seven years *in vivo* to determine if a shift in molecular weight had occurred. It is worth mentioning that direct measurements of molecular weight reduction are the most accurate and reliable method to assess degradation in polymeric materials. Results (shown in Table 1) indicated that “there was no significant difference in molecular weight between the 4-0 PROLENE control and the seven year explant”.<sup>81</sup> The findings from this study are clear. Within the margins of statistical error, none of the implanted sutures suffered any meaningful losses in molecular weight and therefore, by definition, were not degraded<sup>83</sup>.

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<sup>82</sup> Ethicon’s Seven Year Dog Study (ETH.MESH.09888189) pg.117

<sup>83</sup> This observation is also significant because it directly contradicts inferences by Plaintiff’s experts that low molecular weight degradation materials from PROLENE are leaching into adjacent tissue.

Table 1. Molecular weight of exemplar PROLENE compared to explanted PROLENE sutures after 7 years *in vivo*.<sup>84</sup>

	<b>M<sub>w</sub></b>	<b>M<sub>n</sub></b>	<b>PDI</b>
<b>Exemplar</b>	324,000	60,000	4.67
<b>Dog # 2007 site 1</b>	322,000	69,000	5.13
<b>Dog # 2007 site 6</b>	323,000	63,000	5.54
<b>Dog # 1995 site 3</b>	327,000	59,000	5.17
<b>Dog # 2019 site 3</b>	331,000	64,000	5.82
<b>Dog # 2019 site 2</b>	332,000	57,000	6.08

Inherent viscosity tests of ETHILON and Novafil sutures were performed on samples from the seven year study period and compared to data from one and two year samples. The inherent viscosity of a polymer is directly related to its molecular weight. Obtained data showed no change in inherent viscosity in either type of suture after 1-2 years *in vivo* residence. However, after seven years the values ranged from 75% to 93% of those in the one and two year study period for the ETHILON sutures and 75% to 90% for the Novafil sutures.<sup>85</sup>

A polymer's mechanical properties are directly influenced by its molecular weight. When a polymer experiences chemical degradation, including oxidation, its polymer chains are cleaved and reductions in molecular weight are realized. From a bulk physical property standpoint, chemical degradation/molecular weight loss generally results in embrittlement of the material. Embrittlement is best described as a decrease in a material's elongation-at-break, ductility<sup>8</sup> or toughness (area under the stress-strain curve) meaning that the material's ability to stretch, prior to fracturing, has been reduced (Figure 7). Quantifiable changes or shifts in a material's ductility due to degradation are easily computed by performing tensile tests on control and degraded specimens.

In contrast, a polymer's ductility and toughness can increase as a result of plasticization. Plasticization of polymers is well documented in the scientific literature and occurs when low

<sup>84</sup> Ethicon's Seven Year Dog Study (ETH.MESH.09888218 – 09888222) pg.146-150.

<sup>85</sup> Ethicon's Seven Year Dog Study (ETH.MESH.09888188) pg.116.

molecular weight compounds diffuse from an external source into the bulk polymer and physically change the intermolecular forces between polymer chains.<sup>86</sup> Specifically, plasticization of a polymer will result in a decreased modulus, increased elongation at break, and decreased breaking strength. Of equal importance is that plasticization is not a chemical degradation mechanism and does not, itself, result in a reduction of molecular weight.

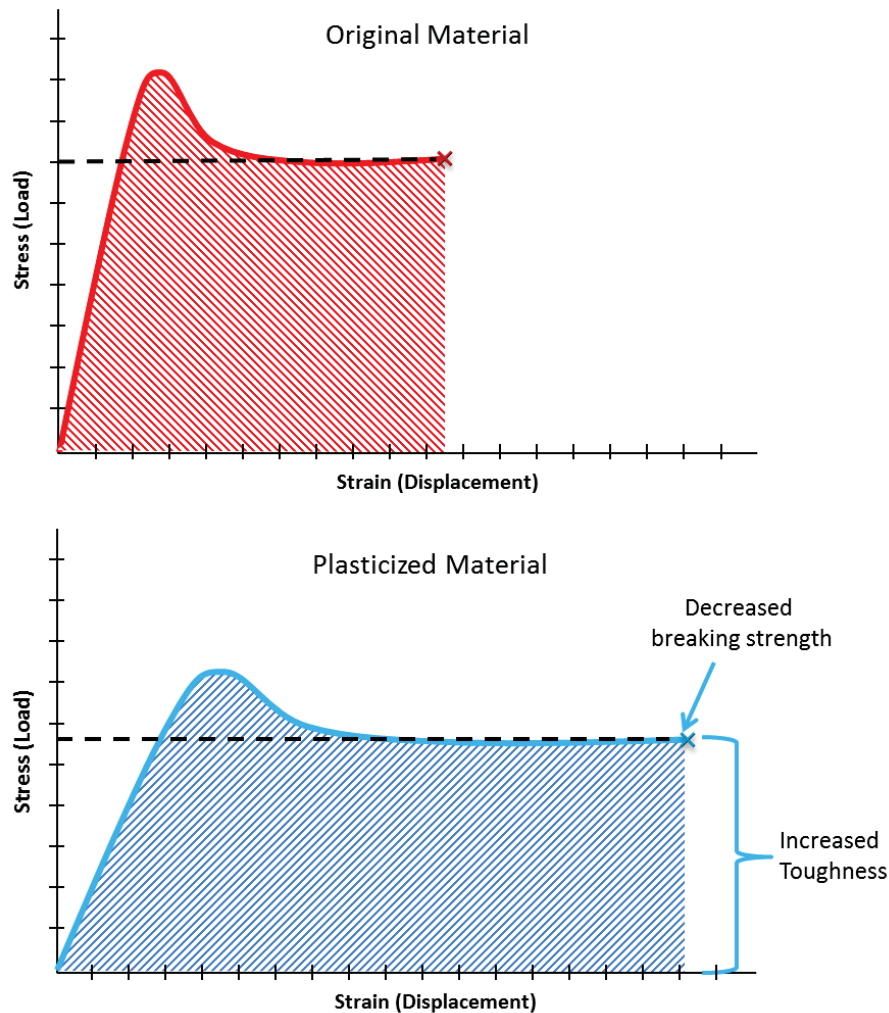


Figure 7. Schematic stress-strain curves for a non-plasticized and a plasticized material. Note the increase in toughness (area under the stress-strain curves) due to plasticization.

<sup>86</sup> Wypych, G. *Handbook of Plasticizers*. Burlington: Elsevier Science, 2013.

In addition to the molecular weight analysis, Ethicon evaluated the mechanical properties of explanted sutures from the seven year dog study to further determine if the bulk physical properties of the PROLENE material were being degraded during implantation. Tensile testing of sutures was performed on both pristine unimplanted and explanted sutures to evaluate the effect of implantation time on the mechanical properties of the suture material. The resulting breaking strength, elongation at break, and Young's modulus are summarized graphically in Figure 8. These tests revealed that ETHILON and Novafil sutures exhibited the greatest decrease in breaking strength, with a 37% and 14% decrease respectively.<sup>87</sup> Furthermore, the physical appearance of the ETHILON sutures was reported as "fragile and worn out with spotted surface."<sup>88</sup> Conversely, "no significant change after seven year (sic) of implantation"<sup>88</sup> in breaking strength was reported for both PROLENE and PVDF sutures.

The elongation at break reported for all explanted suture types increased after seven years and can be seen in Figure 8. The most dramatic elongation *increase* was reported in PROLENE samples, which exhibited a 111% increase over pristine, non-implanted control samples.<sup>87</sup> A dramatic increase in ductility, in conjunction with a reduction in modulus (stiffness) is not indicative of degradation or oxidation, but instead confirms the PROLENE material's ductility and toughness *improve* as a function of implantation time and the improvement is most likely attributed to *in vivo* plasticization.

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<sup>87</sup> Ethicon's Seven Year Dog Study (ETH.MESH.11336183) pg.155.

<sup>88</sup> Ethicon's Seven Year Dog Study (ETH.MESH.11336181) pg.153.

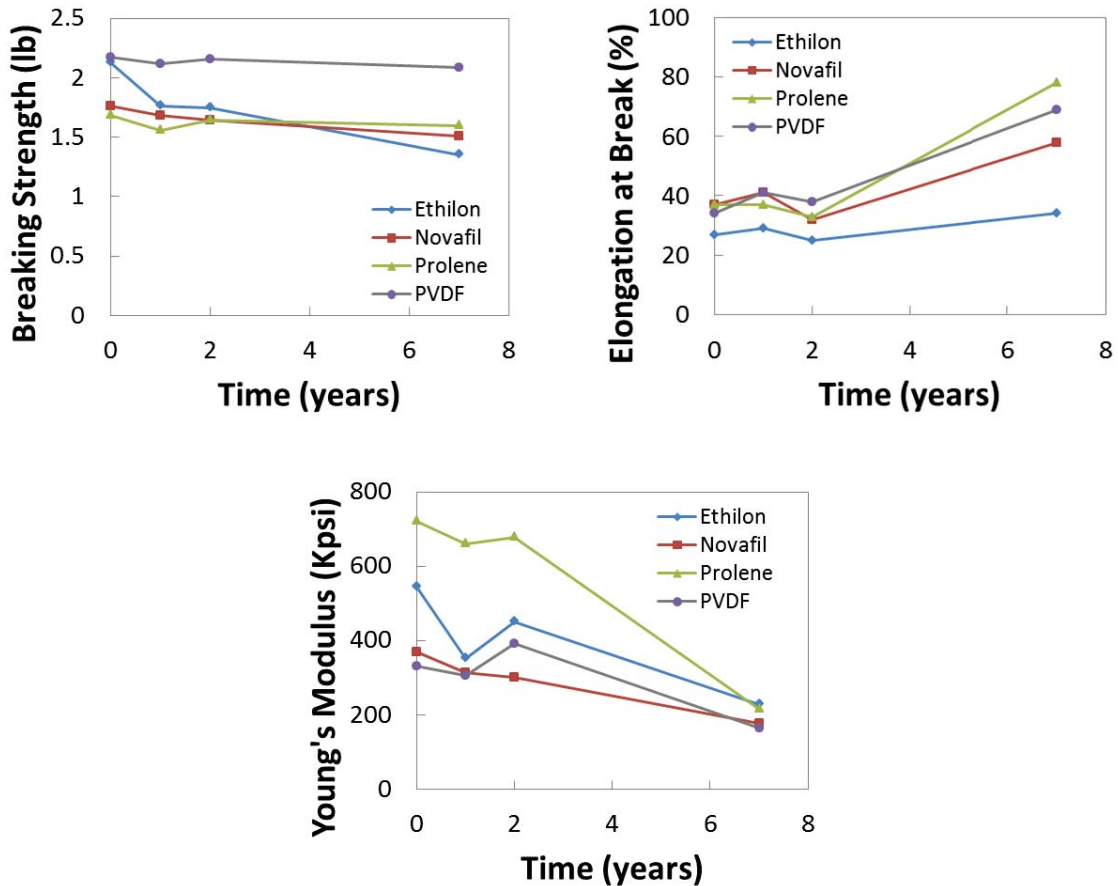


Figure 8. Summary of tensile tests performed on ETHILON, Novafil, PROLENE and PVDF sutures in Ethicon's seven year dog study.

Surface examinations of one suture of each type from each site were performed using both OM and SEM. Microcracking and/or damage was observed on the surface of the sutures as summarized in Table 2. Cracking was considered the most severe and widespread on ETHILON sutures, and was observed after one year *in vivo*. The presence of cracks on explanted Novafil sutures did not follow a clear trend, as seen in Table 2. After seven years *in vivo*, transverse cracking was not observed to a high degree on the Novafil sutures, although other signs of surface damage such as longitudinal scratches and a longitudinal crack were observed.<sup>85</sup> Transverse cracking was not observed on the surface of PROLENE sutures after one year *in vivo*; however, after seven years the appearance of cracking was reported on the surface of 50%

of the sutures. Throughout the seven year study, only one of the PVDF explanted sutures was reported to have “possible cracks” on the surface.<sup>89</sup>

Table 2. Summary of suture surface examinations. The number of sutures exhibiting damage (transverse cracking, longitudinal cracking, scratches, etc.) and the total number of sutures of each type after one, two, five and seven years *in vivo*.

	1 year <sup>89</sup>	2 years <sup>89</sup>	5 years <sup>90</sup>	7 years <sup>91</sup>
<b>PROLENE</b>	0 of 8	1 of 8	2* of 7	4 of 8
<b>PVDF</b>	0 of 8	1 of 8	0 of 7	1 of 7
<b>ETHILON</b>	7 of 7	5 of 7	8 of 8	8 of 8
<b>Novafil</b>	4 of 7	2 of 7	0 of 8	4 of 7

\* One additional suture revealed cracking only after drying.

## Conclusion

Overall, Ethicon invested substantial resources in their multi-year investigation into the composition of the cracked outer layer observed on explanted PROLENE sutures. Ethicon’s seven year dog study data strongly confirms that PROLENE is not experiencing any meaningful degradation *in vivo*, in fact, the material exhibits more ductility and rupture resistance after long-term implantation.

<sup>89</sup> Ethicon’s Seven Year Dog Study (ETH.MESH.11336081 – 11336082) pg.92-93

<sup>90</sup> Ethicon’s Seven Year Dog Study (ETH.MESH.11336165-11336168) pg.101-104

<sup>91</sup> Ethicon’s Seven Year Dog Study (ETH.MESH.09888191) pg.119

## Rebuttal of Plaintiff Experts

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### Iakovlev

Exponent reviewed the report authored by Dr. Vladimir Iakovlev<sup>92</sup> and disagrees with several of his findings, opinions and methodologies. The following section summarizes the issues encountered with Dr. Iakovlev's reports.<sup>93</sup>

Dr. Iakovlev states that, "Examination reveals a polypropylene degradation layer on the outermost layer of the mesh filaments."<sup>94</sup> Dr. Iakovlev performs absolutely no chemical characterization of the external surface to verify his assertion that the layer is polypropylene, much less degraded polypropylene.

Dr. Iakovlev's assertion that the bark layer is comprised of PROLENE is sheer speculation based on his qualitative observation that the bark illuminates when exposed to polarized light. Any material possessing anisotropic domains has the potential to become visible when examined under polarized light. In fact, Dr. Iakovlev has clearly demonstrated that stained biological material (collagen), with presumably a low degree of molecular order, has the ability to illuminate when microscopically imaged under polarized light. The results from his polarized light experiment, at best and at most, suggest that the bark layer contains crystalline domains (local ordering of molecules) within its structure. In short, these results do not confirm the "bark" layer is synthetic, nor does it conclusively prove the layer is PROLENE.

According to the GPC data generated during the seven year dog study (Table 1), none of the explanted PROLENE sutures exhibited any signs of degradation after seven years *in vivo*. No meaningful differences were observed in any of the molecular weight values between unimplanted control sample material and explanted sample material. Moreover, Dr. Iakovlev has not performed any testing that attempts to quantify losses in molecular weight, which is the

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<sup>92</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf

<sup>93</sup> I have authored an additional report that specifically addresses the alleged staining of PROLENE by Dr. Iakovlev.

<sup>94</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 17.

ultimate determination as to whether a polymer has suffered from any meaningful degree of degradation. Without having generated this data on material from control specimens and explanted specimens, any opinions rendered by Dr. Iakovlev that are related to PROLENE degradation are baseless and, therefore unreliable.

For long-chain, linear polymeric materials such as polypropylene, which is the base material in PROLENE, the term degradation is most often ascribed to a reduction in the polymer's molecular weight, which in turn, results in measurable changes in bulk physical properties such as elongation at break. The data generated by Ethicon during its seven year dog study is both clear and overwhelming. None of the tested PROLENE sutures explanted from the subject dogs showed any signs of molecular weight loss or tensile property loss when compared to control samples.<sup>84,87</sup> In fact, the *in vivo* environment had a positive effect on the PROLENE's tensile properties, in particular, the elongation (also referred to as ductility or toughness) increased over the seven year testing period and ultimately achieved strain-at-break values in excess of 80% (an increase of 111% over unimplanted controls).<sup>87</sup> To put this value in perspective, the PROLENE explanted specimens, on average, almost doubled (1.8X) in length prior to breaking during the tensile test. In contrast, polymeric materials that truly exhibit brittle behavior have strain-at-break values that are less than 2%, meaning they are only capable of extending by a mere 2% of their original length prior to breaking during a tensile test. When the data is viewed in totality, it is clear that the PROLENE did not suffer from material degradation and did not become embrittled.

Dr. Iakovlev also opines that PROLENE mesh becomes brittle and, as a consequence, also becomes stiffer with time spent *in vivo*. These opinions are subjective as they are based solely on Dr. Iakovlev's visual observations of the microcracking and the tactile feel of explanted, and perhaps formalin-fixed, bulk tissue and mesh specimens. Estimating a material's "stiffness" or change in "stiffness" by manually manipulating a specimen is not an accepted scientific method within the material science community. Moreover, Dr. Iakovlev has not performed any testing to quantify any perceived increase in stiffness; therefore these assertions are both speculative and baseless. Scientifically reliable test methods exist that quantitatively assess a material's inherent stiffness, namely tensile testing which determines the stiffness (modulus) of a material

of known dimensions based on load-deflection or stress-strain data. In fact, tensile testing on explanted PROLENE sutures was performed by Ethicon at the one year, two year and seven year time intervals during its seven year dog study.<sup>87</sup> The results of these tests were conclusive; the explanted PROLENE material not only became tougher and more ductile over time, but also became *less* stiff based on the reduction in modulus as a function of time *in vivo*. The results are also in complete contradiction to Dr. Iakovlev's assertion that the "degradation of polypropylene with resultant stiffening of the mesh is progressive over the years."<sup>95</sup>

Dr. Iakovlev opines in a recently publish article that "[a]lthough the degraded layer is thin in relation to the fiber diameter, its circumferential distribution provides the highest mechanical effect on the mesh fibers. Degradation related stiffening of the mesh is expected to increase over time."<sup>96</sup> Dr. Iakovlev also notes that his alleged "bark" layer showed large nanocavities (cracks) that indicate brittleness.

From a fundamental polymer science perspective, Dr. Iakovlev's above-stated opinions are flawed for a number of reasons. First, if we assume, for sake of argument, that the "bark" layer is more stiff then the underlying material, if it is filled with cracks (or nanopores and nanocavities as Dr. Iakovlev calls them), it is by definition discontinuous and therefore mechanistically cannot contribute to an increase in stiffening<sup>97</sup>. Dr. Iakovlev cannot have it both ways, either the material is stiff and uniform and leads to mesh stiffening, or it cracks and forms pores and traps dyes; the two are mutually exclusive. Second, if the polypropylene is actually being broken down into smaller molecules, it will tend to become less stiff, not more. Again, Dr. Iakovlev cannot have it both ways (indeed, by stating degradation into smaller molecules leads to stiffening, Dr. Iakovlev underscores the flawed nature of his reasoning).

Dr. Iakovlev presents a short-term control study to show that formalin will not cause a degraded layer to form on PROLENE mesh. His study consisted of immersing pristine mesh samples in

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<sup>95</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 13.

<sup>96</sup> Iakovlev, V. V., Guelcher, S. A., Bendavid, R. Degradation of Polypropylene *in Vivo* : A Microscopic Analysis of Meshes Explanted from Patients. *J. Biomed. Mater. Res. B Appl. Biomater.*, (2015) 000–000.

<sup>97</sup> Had he chosen to do so, with even a fundamental knowledge of mechanics, Dr. Iakovlev could have easily calculated that a continuous (without his observed pores and cracks) bark of the thickness he has measured could not meaningfully contribute to an increase in mesh stiffness.

formalin for four months followed by embedding in paraffin and staining. Dr. Iakovlev states that this control showed an “absence of degradation after exposure to formalin and chemicals of tissue processing,”<sup>98</sup> due to the fact that a bark layer did not form when a pristine sample was placed in formalin. This control experiment is scientifically useless as he chooses to neglect the potential contribution that biological materials may have on the formation of the “bark” layer. If the “bark” were biologic in nature, it would be necessary to not only expose the fibers to formalin, but also include biological exposure/material to properly explore the experimental design space. Excluding one of the potential experimental factors that may contribute to “bark” formation invalidates the findings from his *in vitro* control experiment. In addition, even if he had included all the necessary components for this control experiment, the time period of this study was approximately an order of magnitude (10x) shorter than the length of time explanted samples are stored in formalin and therefore is inadequate.

Dr. Iakovlev uses the “bark” thickness increases with time *in vivo* as further evidence that the “bark” is degraded PROLENE. In his analysis, he completely ignores the possibility that a biologic material covering the PROLENE mesh could also increase in thickness with time; creating a crust that will correspond in thickness to the biologic material deposited *in vivo*. Furthermore, Dr. Iakovlev does not specify his process for measuring the crust layer on his explants. Histological slides have very few, if any, completely circular fiber cross sections. Unless each measurement was taken at the exact minimum diameter location on each sample, his results will be completely unreliable. The presence of a time-dependent bark thickness is simply not instructive in determining the composition of the bark.

No basis has been provided for Dr. Iakovlev’s suggestion that oxidized PROLENE will stain with hematoxylin and eosin (H&E). He neglects to perform a simple control experiment or provide scientific rational to support his implication that his dying technique is appropriate to differentiate between the purported oxidized PROLENE bark layer and the inner core of the same fiber.<sup>99</sup> This lack of a simple control shows that Dr. Iakovlev’s claims are based on flawed and untested hypotheses. Furthermore, H&E stain will adhere to any material with acidic or

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<sup>98</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 17.

<sup>99</sup> Exponent has performed these control experiments, and they are presented in my report regarding intentional oxidation of PROLENE.

basic functional groups, which are commonly found in biologic conditions. If anything, the staining shows that the crust layer is more likely biologic in nature than oxidized PROLENE.

Dr. Iakovlev further opined that the trapping of histological dyes in ‘nanocavities’ somehow indicates degradation due to a decrease in pore size farther from the outer surface of the crust layer. This experiment is wrought with faults that are contradicted by Dr. Iakovlev’s own report and also suffer from lack of controls. The basis for this experiment is that a dye of smaller size will be able to penetrate further into the bark layer due to the presence of supposed nanocavities that supposedly decrease in size as they approach the PROLENE core. Dr. Iakovlev provides no justification or reasoning that nanocavities would exist on the size scale that would be selective to the size difference of the molecules, nor does he even provide the size difference between the staining molecules. In his limited description of the experiment, which is not fully documented within the report, Dr. Iakovlev again failed to provide any control materials with known pores or with varying conditions to show this size selectivity is even possibly. Additionally, Dr. Iakovlev used multiple stains throughout the course of his investigations, including H&E, which consists of two stains; haematoxylin and eosin. Assuming Dr. Iakovlev’s hypothesis was correct and there were pores capable of size selecting for these stains and assuming chemical adsorption was not occurring, H&E stain would show the same size exclusion as the trichrome stain. This does not happen, however, indicating that the idea of pore size selection based on molecular size is not occurring.

Dr. Iakovlev opines that microcracking of the mesh fibers occurs *in vivo*, but fails to consider the possibility that the microcracking could occur during the explanation process. To the best of Exponent’s knowledge, all observations of surface microcracking by numerous researchers have been made on explanted meshes.<sup>45,49,50,58,59</sup> In addition, an Ethicon study determined that explanted mesh material that was maintained and examined under wet conditions showed little, if any, signs of cracking while wet samples that were allowed to dry under ambient conditions developed cracks. In fact, the report states that the “[s]utures kept in the wet state do no exhibit cracks. Upon drying, cracks appear – this was actually observed happening by drying ‘83-165 6 yr. wet’ on the microscope stage.”<sup>68</sup> It is possible that the microcracking observed by Dr.

Iakovlev in TVT mesh “immediately after explantation from the body”<sup>100</sup> resulted from exposure to ambient conditions, mechanical stress imposed on the mesh during explantation or a combination of both.

Dr. Iakovlev further opines that the retention of blue particles within the “bark” material covering the blue fibers proves that the bark is degraded PROLENE. Unfortunately he fails to consider an important aspect of the sample preparation procedure which may account for this result. These samples were microtomed, or sliced very thinly with a knife. Although microtoming is a well-utilized specimen preparation technique within the scientific community, it is essential to be aware of the well documented artifacts associated with the procedure. As discussed previously, microtoming has been known to cause tearing or smearing artifacts,<sup>65</sup> cutting defects,<sup>67</sup> structure deformations<sup>101</sup> and other sometimes difficult to identify artifacts.<sup>66</sup> The fact that the majority of the blue particles appear close to the polymer core of each image strongly suggests sample preparation artifacts opposed to the degraded “bark”, as proposed by Dr. Iakovlev. If the “bark” was degraded PROLENE, the entrapped blue particles would be more uniformly present throughout the bark layer and not biased towards the inner surface.

Dr. Iakovlev states, “For nearly a half century, scientists around the world have studied polypropylene, including Ethicon’s Prolene used in TVT product (sic) and have consistently found that polypropylene degrades over time after being implanted in the body.”<sup>102</sup> Dr. Iakovlev uses fifteen journal articles as references for this statement, but many of them have absolutely no relevance to *in vivo* oxidation of polypropylene. For example, the articles written by Schmidt<sup>103</sup>, Rosa<sup>104</sup>, and Blais<sup>105</sup> report on the *photo* oxidation of polypropylene, these

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<sup>100</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 17.

<sup>101</sup> Morgan, C. “Some Effects of the Microtome Knife and the Electron Beam on Methacrylate-Embedded Thin Sections.” *J Biophys Biochem Cyto*, (1956) 2(4 Suppl):21–28.

<sup>102</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 8.

<sup>103</sup> Schmidt, H., Witkowska, B., Kaminska, I., Twarowska-Schmidt, K., et al. “Comparison of the Rates of Polypropylene Fibre Degradation Caused by Artificial Light and Sunlight.” *Fibres Text. East. Eur.*, (2011) 19(4):53–58.

<sup>104</sup> Rosa, D. S., Angelini, J. M. G., Agnelli, J. A. M., Mei, L. H. I. “The Use of Optical Microscopy to Follow the Degradation of Isotactic Polypropylene (iPP) Subjected to Natural and Accelerated Ageing.” *Polym. Test.*, (2005) 24(8):1022–1026.

<sup>105</sup> Blais, P., Carlsson, D. J., Clark, F. R. S., Sturgeon, P. Z., et al. “The Photo-Oxidation of Polypropylene Monofilaments: Part II: Physical Changes and Microstructure.” *Text. Res. J.*, (1976) 46:641–648.

articles in no way support Iakovlev's statement that polypropylene degrades *in vivo*. The use of irrelevant references at best shows Dr. Iakovlev's lack of polymer science education, training and experience and, at worst displays an attempt to artificially bolster his opinion with misleading references.

## Jordi

Exponent reviewed the report authored by Dr. Howard Jordi<sup>106</sup> and disagrees with several of his methodologies, findings and opinions. In particular, issues were found in both Jordi's interpretation of literature as well as his own research. The following section summarizes these issues.

Dr. Jordi carried out FTIR measurements on three samples (a TVT PROLENE explant, a pristine PROLENE fiber, and human albumin) to identify the presence of specific chemical functional groups which are indicative of oxidation in the explanted sample. He claims that the explanted sample contains oxidized regions of PROLENE based on the presence of an absorbance peak at  $1761\text{ cm}^{-1}$ , which he attributed to carbonyl functionality. However, he does not discuss the amide I and amide II peaks that are clearly present at  $1650$  and  $1550\text{ cm}^{-1}$  respectively, which also appear for the human albumin sample and are indicative of the presence of biological material. Amide bonds are inherent to proteins and are the units that link multiple polypeptides together; many biological materials would be expected to have the presence both of these amide peaks as well as a carbonyl peak. In addition, Dr. Jordi attributes a peak at  $1761\text{ cm}^{-1}$  as evidence of oxidation; however, he does not discuss how he differentiates this peak from the peak associated with the carbonyl containing groups in fatty acid esters which Dr. Jordi claims have "absorbed into the TVT devices."<sup>107</sup>

There are several instances in which Dr. Jordi fails to mention, reference or explain figures that are in his report. One such example can be seen in Figure 8, it is unknown what, if any, conclusions are intended to be drawn since the sample description, procedure used and observations are absent. If it is Dr. Jordi's intention to demonstrate the presence of oxidation in

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<sup>106</sup> Jordi FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf.

<sup>107</sup> Jordi FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 23.

this sample from the FTIR absorbance peak observed at  $1740\text{ cm}^{-1}$  peak, then this conclusion is unsupported since, as discussed previously, he has not provided a method to differentiate between other sources of carbonyl containing functional groups which may be present on or in the explanted PROLENE fibers.<sup>8</sup>

Dr. Jordi used Nanothermal analysis to attempt to determine the surface melting point of pristine and explanted PROLENE mesh fibers. Part of the commonly accepted procedure when using this technique, is to calibrate the temperature of the cantilever as a function of resistance. Dr. Jordi calibrated the cantilevers utilized in this experiment using the melting points of polyethylene terephthalate, polyethylene and polycaprolactone.<sup>108</sup> His justification for using these samples as calibration standards was his reference to Nelson, *et al.*<sup>109</sup> However, based on their work in determining a proper calibration procedure, Nelson *et al.* state that “the use of organic melting standards is thus ineffective for temperature calibration of silicon-heated cantilevers having extremely sharp tips.” Since Dr. Jordi’s referenced calibration procedure directly states not to use the sample type Dr. Jordi indeed uses for his calibration, the calculated melting point values cannot be relied upon as accurate. It is unclear what the offset from the reported values should be since the relationship between bulk and surface melting temperatures is nonlinear.<sup>109</sup>

Even if the values reported by Dr. Jordi are accurate, the conclusion drawn from them is incorrect. Dr. Jordi reported an average melting temperature of the Bellew explanted samples of  $124\text{ }^{\circ}\text{C}$ , compared to  $176\text{ }^{\circ}\text{C}$  for the pristine non-explanted control samples. According to Dr. Jordi, the over  $50\text{ }^{\circ}\text{C}$  decrease in observed melting temperature can be considered proof of sample oxidation. This is incorrect for two reasons. First, surface oxidation of a fiber would result in a decrease in molecular weight. An isotactic polypropylene sample with a melting temperature of  $124\text{ }^{\circ}\text{C}$  would correspond with a  $M_n$  of roughly 4,500.<sup>110</sup> A decrease in molecular weight of this magnitude of the surface material would be apparent in bulk molecular weight

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<sup>108</sup> Jordi Bellew Report - Bellew Report FINAL.pdf.

<sup>109</sup> Nelson, B. A., King, W. P. “Temperature Calibration of Heated Silicon Atomic Force Microscope Cantilevers.” *Sens. Actuators Phys.*, (2007) 140(1):51–59.

<sup>110</sup> Natta, G., Pasquon, I., Zambelli, A., Gatti, G. “Dependence of the Melting Point of Isotactic Polypropylenes on Their Molecular Weight and Degree of Stereospecificity of Different Catalytic Systems.” *Makromol. Chem.*, (1964) 70(1):191–205.

measurements of the explanted samples. If one assumes that the cracked region has a depth of 4  $\mu\text{m}$ <sup>92,111</sup> and is uniformly distributed over the surface of 5-0 sutures as seen in the seven year dog study (suture diameter of 0.1 mm), then the bulk PROLENE  $M_n$  should drop from 60,000 in the pristine sample<sup>84</sup> to approximately 51,000 (see Figure 9). However, from the bulk molecular measurements made in the seven year dog study, it is known that the molecular weight of explanted sutures is  $61,000 \pm 6,000$ .<sup>84</sup> Since the molecular weight according to Dr. Jordi is below the statistically predicted range of values, it is unlikely that oxidation is the cause of the melting temperature drop. The second issue with his conclusion is that Dr. Jordi does not consider alternative explanations for this decrease. The decrease in melting temperature could also be caused by tissue or small molecule plasticizers<sup>86</sup> that are preferentially on or adhered to the outside diameter surface of the fiber, but this was never explored by Dr. Jordi.

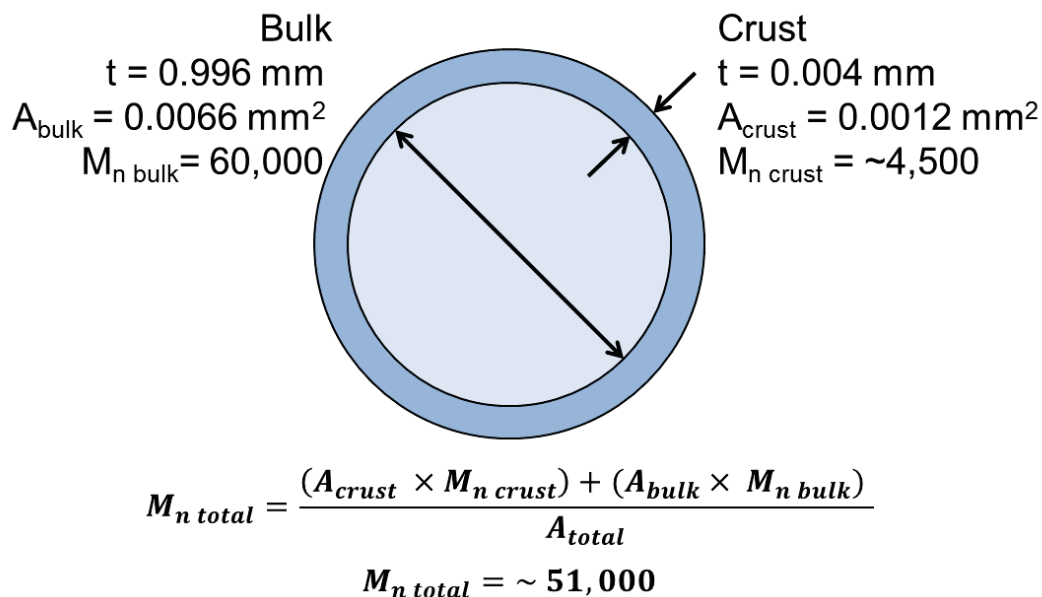


Figure 9. Cross-sectional schematic and calculated theoretical total molecular weight ( $M_n$ ) of excised 5-0 PROLENE sutures from Ethicon's seven year dog study using Dr. Jordi's surface melting temperature to calculate  $M_n$  of the crust layer (note: dimensions are not to drawn to scale).

Dr. Jordi reviewed Ethicon's internal documents, including the seven year dog study, and concluded that PROLENE degrades *in vivo*. While these documents have already been

<sup>111</sup> 11 – "Crack Depth in Explanted PROLENE Polypropylene Sutures" memo 1982.06.15 (ETH.MESH.12831405-12831406).

discussed in the body of this report, several statements from Dr. Jordi were found to be in error and will be discussed herein.

In the process of summarizing Ethicon's documents, Dr. Jordi highlights FTIR data taken by Ethicon, in which Ethicon mentioned the possibility that a weak peak at  $1650\text{ cm}^{-1}$  could be attributed to slight oxidation. However, in the very next paragraph of Dr. Jordi's report, he contradicts his observation, stating "[t]he  $1650\text{ cm}^{-1}$  and  $1540\text{ cm}^{-1}$  bands are typically indicative of what are known as the amide-I and amide-II bands respectively of the polyamides."<sup>112</sup> These bands, as discussed above, in this context, are suggestive of proteins or other biological materials.

Dr. Jordi believes that a "polypropylene mesh placed in the pelvic region of a woman's body will undergo greater degradation than polypropylene placed in the heart of a dog."<sup>112</sup> His basis for this opinion is several articles discussing the bacterial concentrations typically found in this part of the body. But in order to make such a statement, Dr. Jordi would need to compare this environment with that of the heart of a dog. He makes no such comparison and his opinion is not based on scientific facts.

Dr. Jordi analyzed the cracked regions of explanted TVT devices through SEM imaging to demonstrate that fibers had undergone oxidative degradation. However, Dr. Jordi did not remove the biological material from his samples, which can clearly be seen in Figures 11, 12, and 14. As such, he does not account for the fact that the cracked surface may in fact be biological in nature. Furthermore, Dr. Jordi does not present data that identifies the composition of the cracked regions (EDS, FTIR, GPC, or Nanothermal analysis). Therefore, while visual observations can be made from these images, no definitive conclusions regarding the composition of the cracked material can be drawn.

Dr. Jordi further opines that the antioxidant DLTDP leaches with time, his sole evidence is from intensity differences in FTIR measurements conducted by Ethicon. As discussed in detail in the Microcrack Committee Investigation section, an independent analysis of the FTIR spectra

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<sup>112</sup> Jordi FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 14.

would lead to the conclusion that it is impossible to isolate spectral contributions from DLTDP since the carbonyl peak could also be due to proteins.

Dr. Jordi makes the unsubstantiated claim that “a vast majority of scientists who have studied polypropylene for degradation have consistently concluded that polypropylene (including PROLENE) undergoes *in vivo* degradation”<sup>113</sup> by failing to cite the documents with which he makes this conclusion. In fact, since it has been shown that Dr. Jordi draws incorrect or overreaching conclusions of his own research presented in his expert report, it cannot be expected that his review of the scientific literature would lead to an equally valid conclusion.

Dr. Jordi states in his final opinions that *in vivo* degradation causes PROLENE to become brittle. However, he never once discusses the topic of embrittlement in the main text of his report, nor does he perform or cite any mechanical testing to support his opinion, which leaves it unclear as to how this conclusion is reached. Furthermore, this opinion is completely contradictory to the results of the tensile testing experiments presented in Ethicon’s seven year dog study.<sup>87</sup>

Another of Dr. Jordi’s final opinions is that somehow, the manufacturing process leaves PROLENE susceptible to environmental stress cracking. It is unknown on what Dr. Jordi bases this statement, since there is no mention of the manufacturing process in the text of his report, and thus this opinion is completely unsupported.

In Dr. Jordi’s final opinion, he opines that cholesterol and fatty acids absorbed by the PROLENE mesh leave it susceptible to environmental stress cracking. His entire basis for this claim is his reference to Clavé’s own conclusion that “the diffusion of organic molecules into the polymer (especially esterified fatty acids or cholesterol) *may* (emphasis added) be a cause of the polymer structure degradation.”<sup>45</sup> Dr. Jordi fails to perform any original research on this topic and relies solely on conjecture and hypothesizing to form his opinions and therefore his opinion should not be considered scientifically valid.

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<sup>113</sup> Jordi FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 23.

## Guelcher

Exponent reviewed the report authored by Dr. Scott Guelcher<sup>114</sup> and disagrees with several of his opinions. In this report, Dr. Guelcher does not perform any experiments, but instead relies on a small-scale study he previously conducted, and others' studies to form his opinions. In particular, he relies on the works of Liebert,<sup>57</sup> Fayolle,<sup>115</sup> and Oswald.<sup>116</sup>

Dr. Guelcher equates the observed cracked layer covering the exterior of the explanted mesh fibers with embrittlement and degradation. In fact, when referencing Ethicon's internal documents he states, "These documents report evidence of chronic inflammation, oxidation, and degradation (referred to as micro-cracking in the Ethicon documents) of Prolene sutures,"<sup>117</sup> when in fact, micro-cracking and degradation should not be treated as synonyms. In doing so, he has ignored the possibility that the cracked outer layer is something other than oxidized PROLENE without demonstrating any chemical or physical data supporting his accusation of *in vivo* embrittlement.

Dr. Guelcher correctly points out that in a study by Fayolle<sup>115</sup> on thermal oxidation of polypropylene films a reduction in the elongation at break was observed after only 150 hours of ageing while an increase in carbonyl and hydroxyl concentration was detected after 250 hours (induction time). It was also shown that the polypropylene films demonstrated reduced molecular weight after approximately 150 hours. These results demonstrate that when polypropylene is subjected to oxidative degradation the polymer's elongation at break and molecular weight should both decrease and be detectable prior to the detection of any increase in carbonyl or hydroxyl groups by FTIR. In contrast, in Ethicon's seven year dog study, Ethicon's scientists demonstrated that there was no significant difference in molecular weight of PROLENE sutures implanted for seven years compared with controls and that the sutures demonstrated an increases elongation at break after seven years *in vivo*. These results suggest

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<sup>114</sup> Guelcher FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf.

<sup>115</sup> Fayolle, B., Audouin, L., Verdu, J. "Oxidation Induced Embrittlement in Polypropylene — a Tensile Testing Study." *Polym. Degrad. Stab.*, (2000) 70(3):333–340.

<sup>116</sup> Oswald, H. J., Turi, E. "The Deterioration of Polypropylene by Oxidative Degradation." *Polym. Eng. Sci.*, (1965) 5(3):152–158.

<sup>117</sup> Guelcher FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 9.

the PROLENE is undergoing plasticization, not degradation. Dr. Guelcher presents no evidence that conclusively demonstrates that the observed cracking is degraded PROLENE or that the “degradation” is detrimental to the bulk physical properties of the mesh.

Dr. Guelcher’s example of the degradation of poly(ether urethane)s (PEU) used as pacemaker lead insulation is not relevant to the discussion of alleged PROLENE oxidation *in vivo*. PEU and PROLENE are completely different polymers; PEU is a segmented elastomer and PROLENE is a polyolefin. Their chemical composition, polarity, polymerization chemistry, mechanical properties and likely their antioxidant packages are all dissimilar. Hence, there is no reason to believe they would behave similarly or encounter the same failure mechanism *in vivo*. This is supported by Dr. Guelcher’s own results. As mentioned previously, Dr. Guelcher attempted to simulate oxidative degradation of PROLENE using an H<sub>2</sub>O<sub>2</sub> solution enriched with CoCl<sub>2</sub>; however, the resulting morphology of the fiber looked nothing like PROLENE mesh explants, further emphasizing the fact that conclusions cannot be extrapolated from PEU to PROLENE.

Likewise, Dr. Guelcher includes a reproduced plot from an article written by Oswald,<sup>116</sup> of the intrinsic viscosity of *unstabilized* polypropylene at room temperature. The viscosity remains constant until approximately 500 days, where it starts to drop off. This plot is not relevant to PROLENE mesh because as mentioned previously, PROLENE has two different antioxidants (Santnox R and dilaurelthiodipropionate) added to prevent this type of degradation behavior.

Dr. Guelcher opines that “the presence of antioxidants does not permanently protect the TVT mesh against degradation, and thus it is not possible to guarantee that it will perform its intended function after implantation,”<sup>118</sup> yet he fails to produce or cite any literature or testing that supports his opinion that the overall intended “function” of the mesh has been compromised or that it is suffering from a depletion of antioxidants. This statement ignores Dr. Jordi’s finding in

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<sup>118</sup> Guelcher FULL REPORT ETH MDL consolidated Case 8-24-15.pdf, pg 8.

his expert report on the Bellew matter that antioxidants remain in explanted PROLENE mesh even after storage in formalin, which was shown to extract Santonox R from PROLENE.<sup>119</sup>

Dr. Guelcher goes on to claim that the “effects of oxidation on the stability of PROLENE were known to Ethicon prior to launching TVT, but the company did not consider the risks associated with polypropylene oxidation on the stability of the TVT mesh.” This statement completely ignores the years of research conducted at Ethicon into the safety and efficacy of PROLENE. In fact, the development of the TVT device leveraged work on the raw material, PROLENE resin, which began as early as the mid-1960s.<sup>120</sup> Ethicon was very active in “considering” the risks involved in this device and after consideration of these risks Ethicon (and the FDA) determined it was sufficiently safe and effective to market.

Finally, Dr. Guelcher states that Costello<sup>50,120</sup> reported polypropylene mesh oxidation and embrittlement; the conclusions were drawn by comparing pristine and explanted meshes via molecular weight, SEM imaging and compliance testing. This is simply incorrect; Costello never reported the molecular weight of either pristine material or explanted material in either of the two articles cited by Dr. Guelcher. As discussed previously, Costello’s pseudo-compliance testing methodology is flawed and contradicts Ethicon’s testing results. Furthermore, while the SEM images presented by Costello show the presence of transverse cracking, no work was done to identify the elemental composition of the layer, thereby not confirming that the cracked surface is indeed oxidatively degraded PROLENE instead of remnant biological material.

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<sup>119</sup> Jordi Bellew Report – Bellew Report FINAL.pdf, pg 73-74.

<sup>120</sup> Costello, C. R., Bachman, S. L., Grant, S. A., Cleveland, D. S., et al. “Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants From a Single Patient.” *Surg. Innov.*, (2007) 14(3):168–176.

## Conclusion and Opinions

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Based on my analysis, as well as my education, training and experience in mechanics of materials, polymer science and mechanical engineering, I have formed the following opinions to a reasonable degree of engineering and scientific certainty. If additional information becomes available, I reserve the right to supplement or amend any or all of these opinions.

- Based on the tensile testing performed by Ethicon during its seven year dog study, it has been conclusively determined that the PROLENE material becomes more ductile, tougher, and less stiff while implanted.
- Based on the molecular weight analyses performed by Ethicon during the seven year dog study, the PROLENE material is not suffering from any quantifiable degradation while *in vivo*.
- Based on its historical use, long-term testing performed by Ethicon, and retention of bulk physical properties while *in vivo*, PROLENE is a suitable material for implanted mesh devices.
- No reliable scientific evidence has been presented to decisively determine that the “bark layer” is comprised of PROLENE. H&E staining, polarized light microscopy, and melting point analysis are not accepted methods used in the conclusive chemical identification of polypropylene-based materials.
- Plaintiff’s experts’ assertion that the mesh material has degraded *in vivo* is solely based on an observed reduction in melting point as well as visual and microscopic observations of “bark micro-cracking,” which is contrary to scientific principles.
- Plaintiff’s experts’ assertion that the mesh material has become brittle is also solely based on visual and microscopic observations of “bark micro-cracking,” not on

mechanical testing, and is contrary to the scientific findings from Ethicon's seven year dog study.

- Plaintiff's experts' assertion that PROLENE becomes stiffer (less pliable) and resists tissue contraction causing inflammation/pain is based on observed "bark micro-cracking" and tactile feel (a highly subjective assessment). No standardized mechanical testing has been performed to support this subjective assertion. This assertion is contradicted by the mechanical property testing performed by Ethicon and the fundamental principles of mechanics of materials.
- The images presented in the plaintiff's expert report<sup>121</sup> of "freshly excised" cracked PROLENE mesh that has reportedly never been exposed to formalin need to be tempered with Ethicon's findings that exposure to air alone can cause a saline-preserved "wet" explanted fiber to crack in a relatively short period of time. Moreover, the possibility cannot be excluded that mechanical forces applied to the mesh during explantation did not contribute and/or cause the observed cracking.
- There has been no testing performed or scientific literature cited to support the belief that degraded PROLENE is capable of being histologically stained with H&E stains. Therefore, any related conclusions, are scientifically unreliable.

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<sup>121</sup> Iakovlev FULL REPORT ETH MDL Consolidated Case 8-24-15.pdf, pg 83-84.

## **Appendix A**

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### **Steven MacLean, Ph.D., P.E. CV**

#### **Professional Profile**

Dr. Steven MacLean is a Senior Managing Engineer in Exponent's Polymer Science and Materials Chemistry practice. Dr. MacLean's research and professional interests lie in the area of chemical and physical behavior of polymeric materials in end-use applications. His specialties include part design and analysis, failure analysis, and assessing candidate materials through end-use testing. He has studied various polymer failure mechanisms including stress overload, creep rupture, fatigue, environmental stress cracking, and weathering. Throughout his career he has evaluated the suitability of materials for the automotive, sporting goods, medical, business equipment, and construction industries. Dr. MacLean is proficient in a variety of analytical techniques including finite element analysis, statistical methods, as well as empirical approaches to long-term reliability and durability.

Dr. MacLean has considerable practical experience in the conversion of raw materials into finished goods. Throughout his career, he has worked with polymer conversion processes such as injection molding, compression molding, blow molding, extrusion, thermoforming, and laminating. In addition, he has worked on numerous projects involving common secondary operations used throughout the plastics industry such as metallic plating, adhesive joining, painting, as well as vibration and ultrasonic welding.

Dr. MacLean is well versed in voluntary standards and national regulations and codes that often prescribe the technical performance of plastic materials in various industries. Standards organizations and regulatory bodies with which he has interacted include Underwriters Laboratories (UL), International Electrotechnical Commission (IEC), US EPA, California Air Resource Board, NSF International, and ASTM International. He has also participated in numerous sustainability and life cycle assessments (LCAs) per ISO 14040 standards to quantify the environmental impact of manufactured products and raw materials.

Prior to joining Exponent, Dr. MacLean spent 16 years in the plastics industry at General Electric Plastics and SABIC Innovative Plastics where he held several technical positions of increasing responsibility. His activities included material selection and testing for high-demand applications, product safety assessments, failure analysis, and intellectual property analysis.

## **Academic Credentials and Professional Honors**

Ph.D., Materials Science, University of Rochester, 2007

M.S., Materials Science and Engineering, Rochester Institute of Technology, 2001

M.E., Mechanical Engineering, Rensselaer Polytechnic Institute, 1997

B.S., Mechanical Engineering, Rensselaer Polytechnic Institute (with honors), 1993

Tau Beta Pi; Pi Tau Sigma; Society of Plastics Engineers ANTEC Best Paper Award

## **Licenses and Certifications**

Registered Professional Engineer, New York, #16-079001

Registered Professional Engineer, Maryland, #41593

National Council of Examiners for Engineering and Surveying, Record #47204

Certified Six Sigma Black Belt

## **Publications**

MacLean SB, et al. Fractographic examination and tensile property evaluation of 3D printed acrylonitrile butadiene styrene (ABS). Proceedings, ANTEC, 2015.

MacLean SB, et al. Fractographic examination of failures in polycarbonate and polyoxymethylene due to impact, tensile, fatigue and creep mechanisms. Proceedings, ANTEC, 2013.

MacLean SB, et al. Comparison of mass transit material flammability requirements and trends for aircraft and train applications in Europe and North America. Proceedings, ANTEC, 2012.

MacLean SB, et al. Comparison of mass transit material flammability requirements and trends for aircraft and train applications in Europe and North America. Proceedings, EUROTEC, 2011.

MacLean SB, et al. Root cause investigation of cracked polycarbonate blender jars. Proceedings, ANTEC, 2010.

MacLean SB. Plastics, electronics and the environment: How new global regulations affect material choices. Kunststoffe International 2008 Sept; 97–100.

MacLean SB. Plastics, electronics and the environment: How new global regulations affect material choices. Telepati Aylik Telekom 2008 Mar; 74–77.

MacLean SB, et al. Monolayer barrier for small engine fuel tanks. Plastics Technology Online 2007 June.

MacLean SB. Environmental effects of poly(phenylene ether) blends due to long-term exposure to potable hot water. Ph.D. Dissertation, University of Rochester, 2007.

MacLean SB, et al. The effects of recycling and heat history for select high polymers. Proceedings, ANTEC 2001.

MacLean SB, et al. Poly(phenylene ether) engineering thermoplastic provides creep resistance, toughness and fire resistance required for high performance pallets. Proceedings, ANTEC 2000.

## **Presentations**

MacLean SB, Moll J. The importance of polymer structure-property relationships in preventing failure in medical devices. Medical Grade Polymers Conference, Woburn, MA, 2015.

MacLean SB. Fundamentals of plastics fractography. ANTEC, Cincinnati, OH, 2013.

MacLean SB. Challenges associated with replacing metal with plastic. Material Science and Technology Conference, Pittsburgh, PA, 2012.

MacLean SB, et al. Fractography of unfilled thermoplastic materials subjected to common mechanical failure modes. Material Science and Technology Conference, Pittsburgh, PA, 2012.

MacLean SB. Common analytical techniques for failure analysis – A Resin Manufacturer's Perspective. ANTEC, Boston, MA, 2011.

MacLean SB, et al. Plastic failure analysis and prevention expert panel. ANTEC, Boston, MA, 2011.

MacLean SB. Root cause investigation of cracked polycarbonate blender jars. ANTEC, Orlando, FL, 2010.

MacLean SB. Diffusion of potable hot water in poly(phenylene ether) blends. American Chemical Society Conference, Binghamton, NY, 2006.

MacLean SB. Changes in polycarbonate and ABS mechanical properties due to multiple heat histories. Society of Plastics Engineers ANTEC, Dallas, TX, 2001 (with Korzen).

MacLean SB. Yield Improvement for gas assist panels using statistical methods. Society for the Plastics Industry Conference, Vancouver, BC, 2000.

MacLean SB. Design methodologies for metal to plastic conversion. General Electric Plastics Innovation Seminar, Columbus OH, 2000.

MacLean SB. Fundamentals of polymer science. General Electric Plastics Customer Design Workshop, Pittsfield, MA, 1998, 1999.

MacLean SB. Designing for injection molded parts. General Electric Plastics Customer Design Workshop, Pittsfield, MA, 1998, 1999.

MacLean SB. Mechanical behavior of polymeric materials. General Electric Plastics Engineering Workshop, Pittsfield, MA, 1997.

## **Prior Experience**

Director, Global Agency Relations & Product Safety, SABIC Innovative Plastics,  
2007-2011

Global Technical Manager, General Electric Plastics, 2003–2007

Six Sigma Black Belt, General Electric Plastics, 2001–2003

Senior Application Development Engineer, General Electric Plastics, 1998–2001

Plastic Design and Analysis Leader, General Electric Plastics, 1996–1998

Edison Engineer, Lockheed Martin Corporation, (Formerly General Electric Aerospace),  
1994–1996

## **Professional Affiliations**

- Society of Plastics Engineers (Senior Member)
- SPE Failure Analysis & Prevention Group – Board Member and Treasurer
- ASTM D20 Plastics Committee Member

## Appendix B

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### Testimony of Steven MacLean, Ph.D., P.E.

**Workhorse Custom Chassis, LLC** v. Robert Bosch LLC (Marion Superior Court of Indiana), October 2012 (Deposition)

Trice, et al. v. **Toyota Motor Corporation**, et al. (United States District Court – District of Minnesota), August 2013 (Deposition), January 2015 (Trial)

Alberto, et al. v. **Toyota Motor Corporation**, et al. (Genesee County, Michigan), November 2013 (Deposition)

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Nettleton et al. v. **Ford Motor Company** (United States District Court Northern District of California - San Francisco Division), July 2015 (Deposition)

## Appendix C

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- DEPO.ETH.MESH.00006459-DEPO.ETH.MESH.00006461
- DEPO.ETH.MESH.00006462-DEPO.ETH.MESH.00006464
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- Eth.Mesh.15406867
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- Eth.Mesh.15406877
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# **Steven MacLean**

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Handwritten notes for project no. 45702 re: Development of procedure to ____ ____ ____ of cracks in Prolene Suture." Appears to describes method and result from examination of sutures. Investigator ? E. Lindemann [DEPO.ETH.MESH00004761-4766]
Handwritten notes from Dan Burkley lab notebook regarding Gudoin prolene explants (September 22, 1987) (DEPO.ETH.MESH.000000367)
Handwritten notes regarding completion and conclusion from the investigation/examination of 23 Prolene sutures. Second page is dated 02/01/1988 but appears to go with document. Investigator: not legible [DEPO.ETH.MESH00004757-4758]
Human Retrieval Specimens from Dr. Roger Gregory, Norfolk Surgical Group memo1983.03.29 (ETH.MESH.15955440-15955442)
Intra ocular lens, C. Jordan PR. #41001 [ETH.MESH.15958481-8485]
Intraocular lenses, C. Jordan PR. #41001 [ETH.MESH.15958486-8491]
John Karl's January 23, 2003 Memo titled Prolene Resin Manufacturing Specifications and Additive Package (ETH.MESH.02268619)
July 6, 2007 email from Dr. Engel re "How inert is polypropylene?" (ETH.MESH.05447475)
June 15, 1982 memo from Anthony Lunn regarding Crack Depth in Explanted Prolene Polypropylene Sutures (ETH.MESH.12831405-406)
Laboratory Notebook of D. Burkley covering March 20,1984 to October 23, 1984 [DEPO.ETH.MESH00000347 - Ledger and attached slides [ETH.MESH15406846-6977]
Listing of explants, SEM evaluation and SEM number with attached slides containing handwritten information. [ETH.MESH.15406978-6999]
March 12, 2012 Memo re Response to email from Clare Huntington 26 January 2012 regarding publication by Clave et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants" (ETH.MESH.07226481)

Meeting Minutes: TVT Development-Team-Meeting 7.28.1999 [ETH.MESH.08165497-99]
Memo Burkley to A.J. Melveger re: IR Microscopy of Explanted Prolene Received from Prof. R. Guiddin [ETH.MESH 12831391-1404]
Memo by Matlaga, Sheffield & Fetter to P. Marshall re: Human Retrieval Specimens from Dr. Roger Gregory, Norfolk Surgical Group. Samples were submitted from evaluation. The results are included in the memo. [ETH.MESH.1595440-5442]
Memo Dr. Borysko to Melveger et al. re: Examination of 5/0 and 6/0 Cardiovascular Prolene Sutures [ETH.MESH15958410-8432]
Memo Frick to Matlaga enclosing specimens of graft and suture material from two of Dr. Roger Gregory's patients. [ETH.MESH15955443-5452]
Memo from Burkley to J. McDivitt re: Fourier Transform-Infrared Examination of Prolene Microcrack and Photo-Oxidized Polypropylene [ETH.MESH15958336-8395]
Memo Garfield Jones to E.A. Block re: Prolene Polypropylene Suture/Tissue Specimens. Enclosing Prolene suture explants received from Dr. Margaret Billingham with attached letter regarding the sutures. [ETH.MESH 15955472-5473]
Memo Lunn to Melveger re: Crack Depth in Explanted Prolene Polypropylene Sutures [ETH.Mesh 12831405-1406]
Memo Matlaga and Sheffield to Dr. R.L. Kronenthal re: Examination of Prolene (Polypropylene) Sutures from Human Cardiovascular Explants received from Dr. Margaret Billingham for evaluation. The results are included in the memo. [ETH.MESH15955462-5468]
Memo Matlaga to Dr. A. Lunn re: Prolene (Polypropylene) Microcracks. Matlaga reviewed histological preparation from past samples more critically and provided the results. [ETH.MESH15955438-5439]
Memo Matlaga to P. Marshall re: Human Retrieval Samples [ETH.MESH15958400-8404]
Memo Matlaga to R.L. Kronenthal re: Prolene Polypropylene Suture Explant from Dr. Drewes [ETH.MESH15958405-8407]
Memo Moy to A. Melveger re: Prolene Microcrack Experiments [ETH.MESH 15958445-8451]
Memo Moy to A.J. Melveger re: Prolene Microcracking [ETH.MESH15958452-8469]
Memo R.J. Reinhardt to Dr. D.C. Marshall re: Prolene Polypropylene Suture. Included was a dissected surgical specimen of a graft sutured with Prolene suture received from Dr. Richard J. Sanders of Denver, Colorado. [ETH.MESH15955469-5471]
Memo Schiller to T. Davidson et al. re: Polene 7 year explant ERF Accession #84-533 [ETH.MESH15958408-8409]
Memo to Dr. A. Melveger re: Optical examination of 7 /12 year Prolene Explant, ERF Acc. #84-194. Examination results included along with Handwritten notes
Microscopic Examination of Prolene (Polypropylene) Suture and Dacron Graft Returned for Norfolk Surgical Group, LTD (Human Retrieval) (ERF Accession No. 82-147) [ETH.MESH.15958396-839]
NDA – 4.16.1969 PROLENE FDA Approval (ETH.MESH.09625731-09625737)
Page from Prolene IFU re: Degradation
Project No 47201
Prolene – 7 year Explant from Dr. Drewes (ERF Acc. #84-533) [ETH.MESH.15958503-8507]
Prolene Microcrack Experiments.pdf [DEPO.ETH.MESH.00006325-31]
prolene microcracking [DEPO.ETH.MESH.00006386]
Prolene Package Insert re: Degradation (ETH.MESH.09634318)
Prolene Suture (treated and un-treated) (Dr. Guidain) [ETH.MESH.15958478-8480]
PROLENE suture NDA Preclinical Studies.pdf (ETH.MESH.09626242 – 09626359)
PSE 97-0197.pdf (ETH.MESH.05315240 – 05315295)
Quebec Explants - SEM Evaluation [DEPO.ETH.MESH.00004755]
Risk Assessment Summary for Product in the Gynecare TVT Secure System [ETH.MESH.11353422-39]

Satya Garg's November 12,1987 Memo regarding Gudoin prolene explants Study Meeting Minutes 10/8/87 (ETH.MESH.12831407)
Second lolab job – requested by Sal Romano Project #45702-509 [ETH.MESH.15958510-8511]
SEM 10551-10572 83D057-83D960-83D035-84D007-84D010-83D067-83TM020 [DEPO.ETH.MESH.00006332-
SEM 1205-1208 and 1211-1212 and 1215-1216 PROLENE - tissue digestion treatment [DEPO.ETH.MESH.00006340-41]
SEM 4088-4101 Intra-ocular Lens for SR29477 [DEPO.ETH.MESH.00006342-46]
SEM 4102-4117 Intra-ocular Lens for SR29477 [DEPO.ETH.MESH.00006347-52]
SEM 4749-4754 Intra-ocular Lens cracks near haptic for SR29477 [DEPO.ETH.MESH.00006353-55]
SEM 5627-5641 10-0 PROLENE explants [DEPO.ETH.MESH.00006356-63]
SEM 7467-7478 7 year explant ERF 84-533 [DEPO.ETH.MESH.00006364-68]
SEM Negatives 4696-4701 Intra-ocular Lens [DEPO.ETH.MESH.00006369-70]
SEM Negatives 4736-4741 Intra-ocular Lens [DEPO.ETH.MESH.00006371-72]
SEM Negatives 5627-5641 10-0 PROLENE Explants [DEPO.ETH.MESH.00006373-78]
SEM Negatives 5627-5641 10-0 PROLENE Explants [DEPO.ETH.MESH.00006379-84]
Seven Year Dog Study (Lewis trial exhibit no. 1291) (Complete)
Seven Year Dog Study (Used as exhibit at the 30(b)(6) deposition of Thomas Barbolt [ETH.MESH.11336184 - ]
SR14154 10-0 PROLENE explant [DEPO.ETH.MESH.00006385]
Sunoco MSDS (ETH.MESH.02026591)
The Use of Mesh in Hernia Repair by L. Thomas Divilio, MD, FACS [ETH.MESH.14442958-76]
Third type sample from lolab Corp., Intra-Ocular Lens Project #47416 [ETH.MESH.15958508-8509]

<b>Other Materials</b>
American Medical Systems. AMS Large Pore Polypropylene mesh. 510(k) #K033636
American Medical Systems. BioArc TOTM Subfascial Hammock. 510(k) #K040538
ATR – Theory and Applications.pdf Pike Technologies
Boston Scientific Corp. Pinnacle Lite Pelvic Floor Repair Kit. 510(k) #122459
Boston Scientific Corp. Pinnacle Pelvic Floor Repair Kit II. 510(k) #081048
C.R. Bard, Inc. Avaulta™ Solo Support System and Avaulta™ Plus Biosynthetic Support System. 510(k)
C.R. Bard, Inc. Bard® InnerLace™ BioUrethral Support System. 510(k) #K031295
Coloplast A/S. Restorelle™ polypropylene mesh. 510(k) #K103568
EAG FTIR Technique Note
Ethicon, Inc. Gynemesh PROLENE Soft (Polypropylene) Mesh. 510(k) # K013718
Ethicon, Inc. PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh. 510(k) #962530
Island Biosurgical, Inc. Island Biosurgical Bolster. 510(k) #K960101
ISO 10993-1-2009
MentorCorp. Mentor ObTape™ Trans-obdurator Surgical Kit. 510(k) #042851
MLE, Inc. Suture Fixation Device. 510(k) #K021834
Mpathy Medical Devices, Ltd. Minimesh® polypropylene mesh. 510(k) #K041632
Sofradim Production. Parietene™ Duo Polypropylene mesh and Parietene™ Quadra Polypropylene mesh. 510(k) #K072951
Expert Report of Howard Jordi w/ exhibits from a NJ case dated 5.20.14 (under New Jersey cases expert reports)
Expert Report of Vladamir Iakovlev (Iholts)
Expert Report of Vladimir Iakovlev (Richard Schmidt)
Trial Testimony of Vladimir Iakovlev (Cardenas) 8.18.2014
Trial Transcript of Eghnayem v. Boston Scientific 11.6.2014

Expert Reports
Guelcher FULL REPORT ETH MDL Consolidated Case 8-24-15
Iakovlev FULL REPORT ETH MDL Consolidated Case -8-24-15
Jordi FULL REPORT ETH MDL Consolidated Case 8-24-15
Klinge ETH MDL Consolidated Case-Expert Report 8-24-15
Muhl ETH MDL Consolidated Case-Expert Report-8-24-15

## **Appendix D**

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### **Compensation**

In 2015, Exponent charges for my time at a rate of \$355/hour. No portion of my compensation is dependent on the outcome of this matter.